A STUDY OF PREVALENCE OF HELICOBACTER PYLORI IN ACID PEPTIC DISEASE AND ITS SEQUELAE

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CERTIFICATE

This is to certify that this dissertation titled **"PREVALENCE OF HELICOBACTER PYLORI IN ACID PEPTIC DISEASE AND ITS SEQUELAE"** submitted by **DR.K.RAJA RAAJAN** to the faculty of General Surgery, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MS degree Branch I General Surgery, is a bonafide research work carried out by him under our direct supervision and guidance from January 2011 to December 2012.

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CONTENTS

INTRODUCTION

Helicobacter pylori or Campylobacter pylori as earlier known , is possibly the most common human infection. It has been strongly linked to numerous gastro intestinal disorders ranging from non-ulcer dyspepsia to gastric malignancies. There is a wide geographical and ethnic distribution in the infection rate. Certain ethnic groups such as Africans and Hispanics have a much higher rate of infection. In general, people belonging to developing nations have a higher infection rate as compared to their counterparts in developed nations. The epidemiology of Helicobacter pylori infection in India is different from those in developed countries. The main difference lies in the early age of colonization , overt manifestation and high chances of re-infection with the bacteria. It was believed for a long time in the field of medicine that gastroduodenal ulceration was due to high levels of stress but it is now proven that it is this bacterium that lies at the core of causation of acid peptic disorder , gastric malignancies and gastrointestinal lymphoma.

AIM OF THE STUDY

The present study undertaken aims at

1. Determining the prevalence of Helicobacter pylori infection in patients with Acid peptic Disease and its resultant sequelae.
2. Emphasizing the association of Helicobacter pylori with complications of peptic ulcer disease and the need for instituting anti H.pylori treatment for symptomatic cases.

MATERIALS AND METHODS

STUDY SUBJECTS

100 Patients visiting the outpatient Department and those admitted as inpatients in Government Rajaji Hospital , Madurai with complaints of dyspepsia and abdominal pain consistent with Acid Peptic Disease or its resultant acute or chronic sequelae were selected at random. Institutional Ethical Committee Clearance was obtained and Informed Consent was obtained from the study subjects prior to subjecting them to any interrogation or investigation.

METHOD USED

Instant- View^{R} H.pylori Whole Blood/Serum Cassette Test manufactured by Alfa Scientific Designs Inc. was used for serological testing of patients to detect IgG antibodies to Helicobacter pylori. This commercially available kit has sensitivity of 95.1% and specificity of 94.1%. (Information supplied by the manufacturer). The whole blood test and serum test has comparably equivalent results. Upper Gastrointestinal Endoscopy was used to investigate the patients for the pathological process.

TECHNIQUE

One drop of Whole Blood was added to the sample well. 30 seconds is allowed for the sample to get absorbed by the test strip. 3 drops of the provided diluent (PBS diluents with 0.2% sodium azide) is added.

PROCESS

The Test used is a "One Step Immunochromatography" technique. It detects Immunoglobulin type G directed against Helicobacter pylori in the human blood or extracted serum. The method employs a combination of anti-human immunoglobulin dye conjugate and highly purified Helicobacter pylori protein. As the sample flows through the absorbent paper, the anti-human immunoglobulin dye conjugate binds to the IgG antibody present in the sample. This complex binds to H.pylori protein in zone T and produces a coloured band. In the absence of antibodies , only the zone C changes colour due to the binding of unbound conjugate to a reagent fixed in zone C. This indicates proper performance of test but lack of IgG antibodies in the specimen added to the test strip.

INTERPRETATION

If both C line and T line appear, it indicates that IgG antibodies specific to Helicobacter pylori are detected and the result is Positive. If only the C line appears, the result is Negative Strong positive results are seen in 2 to 3 minutes.

Weak positive result can be seen upto 7 minutes. The results are not interpreted after 7 minutes. (Fig. 1 , 2)

PATIENT CATEGORIZATION

- Patients with peptic ulcer type of pain but normal endoscopy were classified as Non-Ulcer Dyspepsia (NUD).
- Those with edema or erythema of the mucosa were categorized as having Gastritis.
- Also included were those patients with proven growth in the distal part of the stomach.

HELICOBACTER PYLORI – THE PATHOGEN

HISTORY

The spiral-shaped micro-organisms were described a century ago by Professor W. Jaworski from Poland. It was discovered in animals by G. Bizzazero. J.R. Warren of Australia who noted spiral bacteria in the stomach. Robin Warren and B.J. Marshall performed a successful culture in 1982 . Initially called Campylobacter pyloridis, it was rechristened as Campylobacter pylori to be more grammatically apt in Latin terminology. Later ribosomal studies showed that the bacteria were not related to Campylobacter genus and hence the new genus Helicobacter was postulated. The name pylori denotes 'of the pylorus' which in Greek means 'gatekeeper'. The Nobel Prize for Medicine was awarded to Barry J. Marshall and J. Robin Warren in 2005 for discovery of the bacterium and its pathological role in human disease. Genetic diversity data suggests that the bacteria had migrated from Africa about 58,000 years ago. This shows millennia of association between humans and Helicobacter pylori. Helicobacter pylori also holds a place of honour as being the first bacteria to be categorized as a Biological Carcinogen.[1]

MICROBIOLOGY (Ref. Fig.3,4)

Helicobacter pylori is a gram -ve helical or curved bacillus. It is about 3 microns long and 0.5 microns in diameter. It is a fastidious, microaerophilic flagellate that has 4 to 6 lophotrichous flagellae which are composed of two types of Flagellins.[2] It contains the enzyme 'Hydrogenase' which oxidizes Hydrogen molecules produced by intestinal bacteria.[3] It is also capable of forming Biofilms.[4] It also has the capability to change into a non-culturable coccoid[5] form to offer survival advantage during adverse conditions. Helicobacter has the following culture needs

- Culture temperature of 37 degree Celsius
- Oxygen concentration of 5 to 10% (Microaerophilic)
- Carbon di oxide concentration of 5 to 12% (Capnophilic)

H.pylori has 5 major outer membrane proteins (OMP). The major one being the family of proteins called Adhesins. The remaining 4 OMP's include Porins, Iron transporters ,Flegellar proteins and some functionally unknown proteins. Common to all Gram – ve Bacteria , H.pylori also has a outer membrane bound Lipopolysaccharide (LPS). The O antigen on this membrane bound gycolipid can become fucosylated and resemble Lewis blood group antigen found in gastric mucosa.[6] This may provide protection from immunological destruction.

GENOMICS

The genetic structure of H.pylori genome is highly geographically oriented both the core components and the flexible genome sequences. The genome sequence of Helicobacter pylori is 1.67 Mb long. Genomic study has revealed the presence of a 40 kb long Cag Pathogenicity island that contains more than 40 different genes that are responsible for the pathogenicity of the bacteria. Absence of this pathogenicity island renders the strain avirulent and its carriers asymptomatic.[7] Biologically active cagA gene leads to aggressive behavior of the bacterium with predisposition to intense ulceration of stomach and duodenum.[8] An enzyme called SRC Kinase phosphorylates CagA protein which leads to activation of SHP2 phosphatase. This substance acts as an oncoprotein. This could be a plausible explanation on events leading to carcinomatous changes in stomach. Based on binding receptor differences, CagA is further divided into East-Asian CagA and Western CagA. The East Asian variant has greater biological activity compared to its counterpart , the Western CagA. Strains with more number of cagA tyrosine phosphorylase are linked to causation of stomach cancers.[9]

Encoded by vacA gene, VacA protein has been proven to be an inducer of apoptosis in epithelial cells. It has been proposed that VacA protein is a potent immunomodulatory toxin. It suppresses local immunological response , thereby delaying the local clearance of the infection leading to persistence of local

infection sans resistance . [10] The cytotoxin suppresses the local activation of immunologically competent T lymphocytes. However , the true involvement of this cytotoxin in the pathogenicity of Helicobacter pylori infection still remains a theory under debate and further research is underway.

Mukhopadhyay et al.conducted a study in Calcutta. They demonstrated more than 70 strains of the bacteria. Among them, more than 90% had in them what is known as the cag Pathogenicity island. This was a much higher prevalence than in the west or even East Asia for that matter.[39]

Horizontal gene transfer and genome plasticity contribute to the evolution of pathogenic variants of Helicobacter pylori. Thus modern day Helicobacter harbours gene pools from ancestral populations that were from different continents and can be correlated with human migration. The laterally acquired genes offer survival advantage to organism in different hosts. The gain of Pathogenicity islands enables today's bacteria to compete with native strains. For example, the South American strains are gradually disappearing and are being replaced by much more aggressive European strains.

EVOLUTION

Helicobacter pylori migrated out of Africa about 58,000 years ago. Its evolution lead to 7 phenotypes. These can be broadly named as Europe (isolated

from Europe and India) , Africa 1 (from Africa), Africa 2 (from South Africa), East Asia , Asia 2 (from North India and Bangladesh), Maori (from Polynesia) and Amerind (from Native Americans). Mixing up of genomes occurred mainly due to colonization and slave trade. The study of genomic structure and evolutionary pattern of Helicobacter pylori has provided humans with extensive knowledge about the pattern of migration and settlement of our ancestors and origins of various races.

There exists a bizarre entity in Helicobacter pylori known as "Microevolution". This indicates evolutionary genomic changes occurring in an organism that is already in a state of active infection in a host. This occurs due to recombinant changes occurring in vivo. Mutation of cagA gene has been demonstrated by Aras et al[11] in two samples taken from the same patient with a time interval of 7 years. Kersulyte et al[12] has demonstrated deletion of cag island due to mutational changes. Such alterations may lead to loss of disease causing capacity.

EPIDEMIOLOGY

Helicobacter pylori is the most widespread infection in the world. Developing countries have a much higher infection rates than Western countries. Also those in developing nations seem to acquire the infection at a much earlier

age than their counterparts in developed nations.[13] Infection at a younger age is likely to result in prolonged inflammation followed by gastric atrophy leading to higher risk of ulcer and cancer. The most important contributing factor responsible for this is the poor sanitary conditions in developing countries. People in the low socioeconomic strata are also prone to infection mainly due to poor sanitation.. Helicobacter has been positively associated with distal gastric adenocarcinoma and MALToma. It also has a negative association with reflux oesophagitis and oesophageal adenocarcinoma. An interesting fact is the recent revelation of involvement of the bacteria with numerous other systemic and auto-immune disorders such as ITP , dermatalogical conditions, hepatocellular diseases and cardiovascular diseases.[14]

MODES OF TRANSMISSION

The bacteria has trophism for gastric type of mucosa and ingestion seems to be the most likely route, though this may occur by means of gastro-oral, Oro –Oral and Faeco-oral routes. Person to person contact is the most accepted mode of transfer. Maternal infection confers 8 times risk and paternal infection carries 4 times risk of the child acquiring infection.[15] The Bacteria can be isolated from the blood, urine, faeces, saliva and dental plaques in infected individuals. The relative risk of infection increases according to the number of children who are reared under the same roof. The emphasis on the same household is because siblings and

concordant twins brought up at separate homes from the time of birth do not show the same relative risk of acquiring the infection

The possibility of transmission between spouses remains controversial. The odds ratio of infection when one partner is infected in around 7.0. It depends on the number of years that they have lived together.[16]

Helicobacter pylori infection is sometimes categorized under Zoonosis. This school of thought arose from a few studies that demonstrated higher rate of infection in workers handling meat products that were raw.[17] However this finding has been under question because of the fact that there may be immune mimicry between antibodies to H.pylori and antibodies against bacteria like Campylobacter jejuni.[18] Dore et al. have shown higher prevalence in shepherds from a country called Sardinia. The same author has recovered H.pylori from sheep's milk suggesting that sheep may be the ancient host of this ubiquitous bacteria. [19] There have also been reports of isolation of the bacteria from rhesus monkeys. Seroepidemiological studies examining relation between owning a pet and a higher H.pylori infection have failed to prove such association.[20]

Even the omnipresent housefly may be a vector for transmission of the organism. However , H.pylori could not be cultured from housefly forced to feed

on human excreta containing Helicobacter, hence the concept of the common housefly being a possible vector for transmission is brought under question.[21]

Drinking water as a source of infection has been under debate. Klein et al. suggested that Peruvian children with unprotected water supply had 3 times the risk of infection compared to those with protected sources.[22] In a Columbian study Goodman et al. showed consumption of raw vegetables increased likelihood of infection.

In contrast to Western studies, a study from Southern China failed to support the above finding as water being a source of infection. No association was found between drinking water and Helicobacter infection. Similarly studies from Korea and Bangladesh failed to support the above association.[23] Sasaki et al. demonstrated presence of Helicobacter DNA in ponds and springs but not in potable water in Japan.[24]

The opponents of the above environmental theory argue that two factors must be taken into account before interpreting the results of DNA detection in natural environment. One, the mere presence of the bacterial DNA does not indicate presence of viable bacteria and secondly, specificity of DNA PCR in the environments were yet to be discovered. When H.pylori is exposed to unsuitable or hostile conditions, it transforms into a non-culturable but viable coccoid form.

However, recent studies have also questioned this hypothesis, claiming that these coccoid forms are non-viable and represent early stages of bacterial cell death.[25]

EVIDENCE FOR GASTRO-ORAL TRANSMISSION

Refluxed gastric juice is considered as a most likely source of infection as upto 58% of infected subjects harbor the bacteria in their gastric juice. Also, there seems to be a higher prevalence of infection among gastroenterologists.[26] Vomiting and regurgitation of food in children maybe an important factor contributing to children being the source of infection. Leung et al. postulated that transmission through vomitus is a possible mode of transmission.[27] Parsonnet et al. conducted a study in which they were able to culture Helicobacter pylori from the vomitus of adult subjects after administering an emetic to induce vomiting. They were also able to culture the bacteria from air samples obtained 0.3 meters away from the subjects when they were vomiting. However samples taken 1.2 meters away failed to yield positive results.[28]

EVIDENCE AGAINST GASTRO-ORAL TRANSMISSION

Numerous attempts at culturing Helicobacter from the oral cavity have failed. However, there are numerous studies in which the bacteria has been cultured from dental plaques. Desai et al. found the presence of Helicobacter pylori in the dental plaques of 98% of his test subjects, Indian dyspeptic patients. His

study was based on Urease Breath Test only. The study was confounded because of the presence of other Urease producing bacteria as part of the normal oral flora. This could point towards the false relationship put forth by this study. One more possibility is that H.pylori could even be a part of the autochthonous microbiota.[35] Another consideration to be kept in mind is the absence of increased prevalence in dentists and dental workers who are constantly exposed.[36]

EVIDENCE AGAINST FAECO-ORAL TRANSMISSION

Though fecal transmission of Helicobacter pylori has been elucidated, there exist certain factors that bring this postulate under question. This bacteria is not adapted for such passage. Infact, there is surmounting evidence that the bacteria is lethally affected by bile. Therefore survival of the bacteria after passage through the bowels is highly unlikely.[37] But in patients who had received purgation prior to testing tested positive for culturability of H.pylori in the stools. The mere demonstration of the presence of Helicobacter pylori DNA in stools by PCR does not indicate presence of viable bacilli.

As an inference , unlike hundreds of other infectious diseases that have been successfully prevented by epidemiological studies and preventive measures, the infection caused by Helicobacter pylori still proves to be an elusive adversary.

Much deeper understanding of its epidemiological profile including modes of transmission are essential prior to any attempts at controlling the disease.

FACTORS INFLUENCING TRANSMISSION

There are two major factors that influence the transmission of Helicobacter pylori. They are Socioeconomic status and Genetic predisposition.

Low Socioeconomic status is strongly associated with infection with the bacteria. An interesting aspect is that the socioeconomic status of the individual during childhood has a strong bearing on the acquisition of infection. Any individual who started at a lower strata has the same risk of infection even after migration to a higher socioeconomic status in adulthood. There is a higher prevalence of infection in economically backward groups settled in developed countries.[29] In a study by Malaty et al. it was found that Blacks and Latin American people settled in USA still had a higher rate of infection prevalence compared to the native population inhabiting the same locality. They also showed that identical twins reared apart had high degree of discordance when tested for H.pylori status.[30]

The only setback with considering the socioeconomic status of an individual as a factor influencing transmission is that this criterion is very broad in the sense that there are numerous contributing factors that are encompassed within it. These

include living conditions, population density and literacy. Higher the density, higher the chance of transmission. Siblings using the same room have increased prevalence.[29]

Another interesting scenario is one in which British soldiers posted in areas with poor hygiene conditions for long periods didnot develop the infection. This further supports the hypothesis that the infection is primarily acquired during childhood.[31] Forman et al. showed the existence of an inverse relationship between educational status and prevalence of H.pylori infection.

Interestingly, there has been a steady decline in the prevalence of infections in countries with evolving socioeconomic conditions like Japan. A similar trend is noted in Korea where there has been a gradual shift in living conditions.

The second factor influencing the transmission of bacteria is Genetic predisposition. High degree of concordance has been demonstrated in identical twins.[32]

ANATOMY OF STOMACH

The stomach, as a J-shaped dilatation of the gastrointestinal tract, located between the oesophagus and duodenum. It functions as a reservoir of food and initiates digestion. Stomach volume ranges from about 30 mL in a neonate to 1.5 to 2L in adulthood. (Fig . 6)

EMBRYOLOGY (Fig.10)

The stomach develops in the fourth week of gestation as a dilatation of the distal foregut. As the stomach enlarges, the dorsal aspect grows rapidly than the ventral part, thus forming the greater curvature. During the development process, the stomach rotates 90 degrees along its longitudinal axis and thus the greater curvature comes to the left and the lesser curvature to the right. The combined effects of rotation and differential growth result in the stomach lying transversely. This also explain the innervation of the stomach: the right vagus nerve going posteriorly and the left one going anteriorly.

GROSS ANATOMY

The oesophago-gastric junction lies to the left of the 10th thoracic vertebra, 1 to 2 cm below the diaphragmatic hiatus. The gastro duodenal junction lies at L1 and generally to the right of the midline . Caudal part of the greater curvature may

extend below the umbilicus when there is stomach dilatation caused by distal or outlet obstruction. The greater curvature comes to the left, the lesser curvature comes to the right. Posteriorly, pancreas, transverse colon, diaphragm, spleen, and apex of the left kidney and adrenal gland form the stomach bed structures. The posterior wall of the stomach forms the anterior aspect of lesser sac. Anteriorly, the liver binds the stomach.

The stomach is completely covered by peritoneum, except for a small area at the gastro esophageal junction. This peritoneum has a double layer that passes from the lesser curvature to the liver as the lesser omentum and then hangs down from the fundus and greater curvature as the greater omentum, extending to the transverse colon as the gastrocolic ligament, spleen as the gastrosplenic ligament, and diaphragm as the gastrophrenic ligament.

The stomach is divided into four anatomical regions. They are the Cardia, Fundus, Body, Pyloric Antrum and the Pylorus. The cardia is that part of the stomach immediately adjacent to the junction with the esophagus. Controversy exists as to the nature, location, and extent of cardiac mucosa. The fundus projects superiorly. It is dome-shaped and is the most superior portion and is in contact above with the left part of the diaphragm. The body is the largest part of the

stomach and is located below the fundus. The incisura angularis is a fixed, sharp indentation that marks the distal aspect of the body . The gastric antrum extends from its indistinct border with the body to the junction of the pylorus and the duodenum. These gross anatomic landmarks correspond roughly with the histology of the stomach. The antral mucosa in reality extends from an area on the lesser curvature somewhat above the incisura.

The pylorus is a tubular structure that connects the duodenum to the stomach and contains the pyloric sphincter. The pylorus is mobile and is usually located 2 cm to the right of midline at the level of L1 vertebra.

VASCULAR SUPPLY AND LYMPHATIC DRAINAGE (Fig.8)

The arterial blood supply to the stomach is derived from branches of the celiac artery—Common Hepatic, Left Gastric artery and Splenic vessels —that form two arterial arcades along the greater and lesser curvatures. The lesser curvature is supplied from above by the Left Gastric artery, a direct branch of the Celiac Axis and from below by the Right Gastric Artery, a branch of the common Hepatic artery. The greater curvature below the fundus is supplied by the left Gastroepiploic artery,a branch of the Splenic artery and from below by the right Gastroepiploic artery,a branch of the Gastro duodenal artery. The right and left

Gastroepiploic arteries usually terminate by completing the greater curvature arcade. The arterial supply to the fundus and proximal part of greater curvature is through the Short gastric vessels originating from the Splenic artery.

The venous drainage of the stomach generally accompanies the arterial supply, emptying into the portal vein mostly. The left and right Gastric veins drain the lesser curvature of the stomach. The right and left Gastroepiploic veins drain the inferior aspect and a portion of the greater curvature. The right Gastroepiploic vein terminates in the Superior Mesenteric vein. There is no gastro duodenal vein. The Left Gastroepiploic vein becomes the Splenic vein and later receives the Short gastric veins.

Most of the lymphatics goes to the celiac nodes. Lymphatic channels anastomose freely in the gastric wall, with lymphatic flow directed into one of four groups of nodes. The inferior gastric region drains into sub pyloric and omental nodes, then the hepatic nodes, and finally in the celiac nodes. Lymphatics from the superior aspect of the greater curvature initially drains into pancreatico splenic nodes and then to the celiac nodes. The lesser curvature region drains into the left and right gastric nodes accompanying their respective vessels and terminates in

celiac nodes. The pyloric portion of the lesser curvature drains into the suprapyloric nodes, hepatic nodes then to the celiac nodes.

GASTRIC INNERVATION

The innervation of the stomach comes from both the sympathetic and parasympathetic nervous systems. The gastric sympathetic innervation arising predominantly from sixth to eighth thoracic spinal nerves whose postganglionic fibers course through the celiac plexus. Accompanying these are afferent pain-transmitting fibers from the stomach and motor fibers to the pyloric sphincter. The parasympathetic innervation is via the vagus nerves, which form the distal esophageal plexus, which gives rise to the posterior and anterior trunks near the cardia. The trunks contain pre-ganglionic parasympathetic fibers, as well as afferent fibers from the viscera. These trunks give rise to celiac and hepatic branches before continuing on slightly to the right of the lesser curvature as the anterior and the posterior nerve of Latarjet. These nerves give rise to multiple gastric branches to the stomach wall, where the pre-ganglionic fibers synapse with the ganglion cells in the submucosal or Meissner's and Myenteric or Auerbach's intrinsic nerve plexuses. From these plexuses, postganglionic fibers are distributed to cells and glands and to motor components of the stomach.

TISSUE LAYERS OF THE STOMACH (Fig.7)

The luminal surface of the gastric wall forms thick, longitudinally oriented rugae, which flatten with distention. Four layers make up the gastric wall: mucosa, submucosa, muscularis propria, and serosa. Mucosa lines the gastric lumen, appearing as a smooth, velvety, blood-filled

lining. The mucosa of the cardia, antrum, and pylorus is somewhat paler than that of the fundus and body. It is within the gastric mucosa that most of the functional secretory elements of the stomach are situated. The submucosa provides the dense connective tissue framework of collagen and elastin. Lymphocytes, plasma cells, arterioles, venules, lymphatics, and the submucosal plexus are also contained within the submucosa. The third tissue layer is the muscularis propria which is a combination of three muscle layers oriented from within out is oblique, circular and longitudinal muscles. The inner oblique muscle fibers course over the gastric fundus, covering the anterior and posterior aspects of the stomach wall. The middle circular fibers encircle the body of the stomach, distally forming the pyloric sphincter. The outer longitudinal muscle fibers course mianly along the greater and lesser curvatures of the stomach. The outermost layer is the serosa which is nothing but a continuation of the visceral peritoneum.

HISTOLOGY

The gastric mucosal surface is composed of a single layer of columnar epithelial cells 20 to 40 mm in height. These surface mucous cells contain basally located nuclei, prominent Golgi apparatus and dense cytoplasm with apically dense mucin-containing membrane-bound granules. The cells secrete mucus in granules, which are released by the process of exocytosis or apical expulsion or cell exfoliation. The primary role of mucus, along with bicarbonate is protection of luminal integrity from "the elements": acid, pepsin, ingested substances, and pathogens. Cellular renewal time for a gastric surface mucous cell is approximately 3 days. There are numerous gastric pits which contain gastric glands. These are the source of various secretory products of the stomach.

Secretions from glands are as follows (Fig.9)

- **Mucus neck glands –** They are located in neck of gastric glands. Cuboidal with basal nucleus. They secrete mucus.
- **Parietal cells –** triangular cells with eosinophilic cytoplasm. Located in neck and partially the isthmus of gastric pit. They secrete Hydrochloric acid and Intrinsic factor.
- **Chief cell –** Located at base of gland . They secrete Pepsinogen
- **Enteroendocrine cell -** part of APUD (neural crest origin) cells. They secrete gastric hormones like gastrin and motilin

ANATOMY OF DUODENUM

The duodenum is the first part of the small bowel . Duodenum is the principal site of iron absorption.The term duodenum takes origin a Latin word meaning "twelve fingers' breadth".

The duodenum is 25–35cm long. It begins at the bulb and terminates at ligament of Treitz.

GROSS ANATOMY

Duodenum is divided into 4 parts.

First part

The first part begins as a continuation of the pylorus. From here it passes laterally to the right then superiorly and finally Posteriorly for a distance of about 2.5 inches, directed inferiorly into superior duodenal flexure. It is intraperitoneal.

Second part

located at level of L3 vertebra and continues into the inferior duodenal flexure.

The Duct of Wirsung and Common Bile Duct end in second part of the duodenum at the major duodenal papilla . The dilatation where the two ducts join and form a common channel before opening into the papilla is known as Ampulla of Vater. Proximal to the major duodenal papilla is the opening of the minor duodenal

papilla which forms the opening of the Accessory Pancreatic duct of Santorini. The major duodenal papilla marks the junction of forgut and midgut.

Third part

The third part of the duodenum begins at the inferior duodenal flexure and crosses to the left. It overlies the right ureter, right gonadal vessels, Vena Cava and Aorta.

Fourth part

The fourth part passes to the left of the aorta. Then, it recurves forwards and terminates at the duodenojejunal flexure . The DJ or duodeno-jejunal flexure is surrounded by a peritoneal fold containing muscle fibres. This is known as the ligament of Treitz.

BLOOD SUPPLY

There are two major vessels supplying the duodenum, They are the Superior and Inferior Pancreaticoduodenal arteries. The former takes origin from Gastroduodenal artery. It is one of the terminal branches. The latter originates from Superior Mesenteric artery. These vessels are nestled within the space between the C-Loop of the duodenum and the head of the pancreas.They form an anastomosis. This route could form a site of collateral between foregut and midgut vasculature.

The venous drainage of the duodenum follows the arteries. Ultimately these veins drain into the Portal Vein either directly or indirectly through the splenic or superior mesenteric vein.

LYMPHATIC DRAINAGE

The lymphatic vessels travel along with the vessels. The nodes are Pancraeticoduodenal, Mesenteric and Coelia nodes. First echelon nodes are the Pancreaticoduodenal and Superior Mesenteric. All lymphatics eventually terminate in the celiac nodes.

MICROSCOPIC ANATOMY

Duodenum contains the same 4 layers that are seen in the remainder of the small bowel--namely, the mucosa which is lined by columnar epithelium. Beneath the epithelial layer lies the lamina propria and muscularis mucosa.All these 3 layers form the mucosa in entirety. The submucosa, the muscularis propria (with inner circular and outer longitudinal layers), and the serosa form the remaining layers. The serosa is nothing but a visceral peritoneal reflection.It is present only along the anterior aspect of the duodenum. The posterior aspect is devoid of any serosal covering. The duodenal mucosa is characterized by the presence of Brunner's glands, which secrete mucus.

PHYSIOLOGY OF GASTRIC ACID SECRETION

Gastric acid secretion happens in several steps. The secretion occurs in the parietal cells of the gastric glands. These produce Hydrochloric acid as well as Intrinsic factor needed for Vitamin B12 absorption. Parietal cells are also known as Oxyntic cells. The 3 major stimuli for secretion are Gastrin, Acetylcholine and Histamine. There are 3 major receptors for each of the above effectors. They are CCK receptor for Gastrin, M3 receptors for Acetylcholine and H2 receptors for Histamine. The three receptors are activated by binding of their stimulatory effector. These may be acting via. IP3-DAG Pathway or cAMP Pathway. Hence cAMP and Calcium form the second messengers in the mechanism of acid secretion by the parietal cells or oxyntic cells of the stomach. The final common pathway in secretion is the H/K ATPase pump system. This is present in the basolateral membrane of parietal cells. It is an active transport anti-porter system. The electrochemical gradient needed for its function is created by active transport of sodium ions into the canaliculi from the cytoplasm of parietal cells. In short, the H/K ATPase pump tries to maintain electrochemical neutrality by actively pumping out Hydrogen ions into the lumen of the stomach. Adenosine Triphosphate are the drive to keep this machinery running constantly.

The peak amount of acid that is stomach is capable of producing is 160mM.This amount of acidity is 3 million times higher than arterial blood. The

lowest pH that can be seen is 0.8. However, the actual pH measurable in reality is 1 to 3 only.

There are several phases of acid secretion :

1. The Basal phase: This is the acid produced during the resting stage . No food is present and no digestive process is taking place.
2. The Cephalic phase: One-third of secretion takes place in this phase.It is brought about by psycho-somatic stimuli like thought of food, smell of food etc. It is vagally mediated through Gastrin. It can be abolished by vagotomy.
3. The Gastric phase: Nearly half of the secretion is here. Entry of food into the stomac produces Accomodation and Receptive Relaxation . This stimulates release of gastric juices both through vagus and through local GI hormones. Caffeine also stimulates parietal cells to secrete acid .
4. The Intestinal phase: Final phase of secretion when chyme passes to the duodenum. Stimulated by acid content and by amino acids.

Basal acid output (BAO) is usually less than 10 mEq/hour

Gastric acid production is regulated by both the autonomic nervous system and several enteric or GI hormones. The parasympathetic nervous system, via the vagus nerve, and the hormone gastrin stimulate the parietal cell to produce gastric acid, both directly and indirectly, through histamine from enterochromaffin

- like cells (ECL). Vasoactive intestinal peptide(VIP) inhibits acid secretion.One more hormone that has similar effect is Secretin.

The production of acid is regulated by positive and negative feedback systems. Four types of cells are involved in this process. They are

- Parietal cells
- G cells
- D cells
- Enterochromaffin-like cells(ECL cells)

Besides this, the endings of the vagus nerve and the intrinsic nerve plexuses also influence the secretion.

Nerve endings in the stomach secrete two stimulatory neurotransmitters namely acetylcholine and gastrin-releasing peptide(GRP) . They act on parietal cells and also through the production of gastrin from G cells and histamine from ECL cells. Gastrin acts on parietal cells by stimulating production of histamine.

Histamine is the positive regulator of acid secretion. Its release is stimulated by gastrin and acetylcholine and inhibited by somatostatin.

PATHOPHYSIOLOGY OF H.PYLORI INFECTION

Helicobacter pylori is a bacteria with trophism towards the gastrointestinal tract , in particular, the stomach and the duodenum. Schwartz's dictum states "No acid-No ulcer". This epithet summarizes the thinking concerning the pathogenesis of peptic ulcer . However the recent dictum is "No H.pylori – No ulcer". 90% of duodenal ulcers and 70% of gastric ulcers are infected with Helicobacter pylori.90-100% of duodenal ulcers heal within 2 months of anti-secretory therapy. The damage to the stomach occurs due to a complex interaction between the organism and the host immune system.. It colonizes the mucosa and attaches to the epithelial surface. A myriad of mechanisms have been proposed as to how this ubiquitous bacilli cause the pathological changes with which they have been intimately linked to.

- Direct mucosal damage due to adherence of the bacteria to the epithelial surfaces (Fig .2)
- Liberation of Vacuolating cytotoxin Vac A which causes vacuole formation within the epithelial cells , thereby leading to cellular damage
- Vac A causing a negative immunomodulatory effect causing suppression of local T cell induced immunological response leading to prolonged intense unopposed infection

- Direct stimulation of release of endogenous host inflammatory mediators such as IL-1, IL-6, IL-7, IL-12 and TNF Alpha from the mucosa
- Urease, produced by the bacteria , splits urea into ammonia in vivo. This ammonia confers local protection or so called buffer from the effects of gastric acids by causing alkalinization and also defers local attack by antibodies.
- Bacterial phospholipase caused degradation of membrane bound phospholipids leading to epithelial injury.
- Antral acidification causes stimulation of Gastrin secretion from antral G cells leading to hypergastrinemia and G cell proliferation.[33]

The antrum is the predominant site of colonization in the stomach.(Fig .3) The pH on the surface of antral glands is well tolerated by the bacteria allowing survival and promoting growth. A subset of infected population develop "Antral-predominant gastritis" characterized by chronic inflammation of the pyloric antrum. These are the people prone to develop duodenal ulcers. With the administration of PPI's , there is inhibition of H-K ATPase mechanism leading to decreased acidity of the antrum causing proximal migration of bacteria to corpus and fundus. This predisposes to intestinal metaplasia of the fundic mucosa leading to increased incidence of Proximal gastric adenocarcinoma.

A second subset of individuals are prone to develop the so called “Corpus-predominant gastritis” the features of which overlap Type A Auto-Immune gastritis. It is these people with corpus predominant gastritis that are more prone to develop distal gastric adenocarcinoma.[38]

Chronic Helicobacter pylori infection has been linked to many other enteric infections such as cholera. It still remains under inquiry as to why a co-evolved bacteria would be pathogenic to humans. It is hypothesizes that an originally harmless commensal , has over time, acquired virulence genes as part of its own evolution from the host and environment. There seems to be an abundance of such laterally acquired genes that per say have no known function but can be linked to inflammatory responses within the host.

TABLES & CHARTS

Analysis of Symptomatology (Ref. Chart 1)

Symptoms	No.of Cases
Pain Abdomen	57
Epigastric Pain	14
Vomiting	13
Heartburn	6
Loss of Appetite	6
Mass Abdomen	2
Hemetemesis	1
Malena	1

Duration of symptoms (Ref.Chart 2)

Duration of Symptoms	No.of Cases
<1 week	37
<6 months	48
6 -12 months	7
>12 months	8

Seropositivity in Symptomatic cases (Ref Chart 3)

Serology	No.Of Cases
Seropositive	61
Seronegative	39

Sex Distribution among Seropositve Cases (Ref Chart 4)

Seropositive	No.Of Cases
Male	29
Female	32

Age Distribution of Positive Cases (Ref Chart 5)

Age Group	No.Of Cases
18-30	14
31-40	11
41-50	13
>50	23

Over the counter medication (Ref Chart 6)

Users	60
Non Users	40

Risk Factors (Ref Chart 7)

Smokers	13
Alcohol Users	9

Prevalence of Helicobacter pylori (Ref Chart 8)

	Positive	**Negative**
Active or Healed Ulcer	29	4
Perforation	22	15
Carcinoma Stomach	6	4
Non-Ulcer Dyspepsia	2	7
Gastiritis	2	7
Duodenitis	0	2

OBSERVATIONS AND RESULTS

Study Design : Descriptive Study

Period : January 2011 – December 2012

100 Patients , 50 male and 50 female who had symptoms of acid peptic disease or its sequelae or dyspepsia , who attended the outpatient Department of Government Rajaji Hospital, Madurai or those who had been admitted as inpatients in Government Rajaji Hospital, Madurai were selected at random and Serological Testing for IgG anti-Helicobacter pylori antibodies was done using a Instant View Qualitative Lateral Flow Immunochromatography Kit which is commercially available and also subjected to endoscopy whenever possible.

Generalized abdominal pain was the most common complaint with which the patients presented (57%) followed by complaints of Epigastric Pain (14%). Hemetemesis and Malena were the least common presentation in our study.(1%)

The duration of complaints in majority of the cases were for less than 6 months(48%) followed by Less than a week (37%) Most of these acute presentations were from Ulcer Perforation which a well known sequlae of Peptic Ulcer Disease.

61 out of the 100 symptomatic cases tested positive for Helicobacter pylori. Among the symptomatic cases 52.4% were found to be female. 23 out of the 61 positive cases were above the age of 50 years (37.7%) followed by 14 out of 61 cases in the age group of 18 to 30 years. Another interesting and also worrisome observation is the prolific use or overuse of over the counter anti-secretory medications by symptomatic cases. 60% of cases described use of such drugs. This sort of misuse causes symptomatic but no permanent cure and also interferes with H.pylori testing. In our study, only 13 cases seemed to smoke and 9 alcohol users. However , no conclusions can be drawn based on this observation since this information is more than likely to be biased , with the patients unwilling to reveal their actual addictive habits in full extent. The following prevalence figures for Helicobacter pylori can be obtained from our study.

Patients with Proven Ulcers	-	29/33	- 87.8%
Patients with Perforation	-	22/37	- 59.5%
Patients with Cancer Stomach	-	6/10	- 60%
Patients with Non Ulcer Dyspepsia	–	2/9	- 22%
Patients with Gastritis	-	2/9	- 22%
Patients with Duodenitis	-	0/9	- Nil

DIAGNOSIS OF HELICOBACTER PYLORI INFECTION

The American College of Gastroenterology recommends testing for Helicobacter in the following scenarios.[34]

- Patients with active ulcer
- A past history of documented peptic ulcer
- Gastric MALToma
- Patients who have undergone surgery for Early Gastric Cancer
- People at risk of developing ulcers or stomach cancers

Mayo Clinic screening criteria for Helicobacter pylori are as follows (Fig.15)

Specific testing should only be performed in symptomatic individuals. Asymptomatic colonization can occur and may cause confusion.

- Active Ulcer Disease
- Past history of Acid peptic disorder
- MALT Lymphoma
- Alarm features
- Test and Treat
- < 45 years old dyspeptic cases

Alarm features include GI bleeding, anemia, weight loss, persistent vomiting. In such situations the patient should be directly submitted for endoscopy and evaluation.

Widespread testing for H.pylori is not recommended because of the insufficient evidence in cost-benefit advantage in prevention of associated diseases, possibility of inducing antibiotic resistance and potential negative effect of eradication.

Conditions where evidence is inconclusive for diagnosis and treatment of Helicobacter pylori are ,

- Investigated Non-Ulcer Dyspepsia
- With NSAID use
- Gastro-Esophageal Reflux Disease
- Population at risk for gastric cancer
- Inexplicable pallor in an elderly patient
- Idiopathic Thrombocytopenic Purpura

NSAID and H.PYLORI Eradication

- Eradication does not prevent ulcer formation
- Eradication does prevent ulcer bleeding complications to some extent

- Ulcer recurrence and re-bleeding from ulcer are reduced
- Patients on long-term low-dose aspirin therapy should be evaluated and treated if necessary to prevent complications

Diagnostic tests can be broadly classified into

- Invasive
- Non- Invasive Tests

The Tests commonly in use for detecting presence of Helicobacter pylori are ,

- Blood Test
- Breath Test
- Stool Test
- Urine Test
- Endoscopic Testing – Biopsy and microscopy (Fig. 9)

  Biopsy and Rapid Urease Test (CLO Test)

  Biopsy and Culture

SEROLOGICAL TESTING

IgM levels increases in active infection. It appears within 21 days of exposure. IgA is more specific in children. However , overall IgM and IgA lack the sensitivity of IgG and hence have limited clinical value in screening. IgM is more useful to evaluate effectiveness of therapy. Screening for IgG has the best overall sensitivity

and specificity. It is useful for mass screening purposes. The main advantage is that it can be held reliable even in cases taking PPI unlike most other tests. Samples can be easily obtained.

Disadvantages are

- it cannot be used to demonstrate eradication of infection.
- False positive tests are common in low prevalence populations
- Positive results should be confirmed by other modalities

Bayes' Theorem holds true in sero testing. It states that when the prevalence of a disease is low, the chances are that the diagnostic test will show false positives. Therefore serological testing has low positive predictive value in low prevalence populations.

UREASE BREATH TEST

The Urease Breath test is a rapid diagnostic test. It relies on the fact that urease present in H. pylori breaks down urea to ammonia and carbon dioxide. Urease breath tests are recommended as a preferred non-invasive test for detection and also for evaluation of H.pylori status after completion of treatment.[56]

Patients swallow urea labeled with either radioactive carbon-14 or non-radioactive carbon-13. [57] In the subsequent 30 minutes, the detection of

radioactivity in the exhaled breath is indicative of presence of urea that was split; this indicates that the enzyme urease which is a characteristic feature of the bacteria Helicobacter is present in the stomach.

As two types of urea are used, specialized equipment are needed for evaluation. C-14 is normally measured by scintillation and Carbon-13 by mass spectrometry. Samples are sent to a laboratory for analysis. Mass correlation spectrometry can be performed as an office test since breath samples are continuously collected, and results are provided immediately within minutes.

Comparison between the values obtained before and after the test is done. This is compared to a cut-off value and results declared. The determination of the cut-off value requires usage of many different detection techniques.The value is chosen based on the best combination of sensitivity and specificity.

The test detects active infection. Intake of acid suppression drugs such as PPI or antibiotics such as Amoxicillin causes error in results. Hence this test is useful only after 2 weeks of stoppage of drugs or 2 weeks after completion of treatment regimen.

Some say that H.pylori in dental plaques interfere with results.[57]

The disadvantages are

- It is expensive
- Specialized equipment are needed to assay the carbon dioxide analyte
- Infrastructure is needed to safely handle radioactive materials

ENDOSCOPY (Fig 11 to 16)

Endoscopy is an invasive investigation and is recommended in

- asymptomatic individuals more than 45 years age
- Any patient with alarm features.

The specimen obtained by biopsy is stained with special stains. Some of them are

- Gram stain
- Giemsa Stain
- Silver stain
- Immonostains

Endoscopy has more than 95% sensitivity and specificity. Multiple biopsies increases the accuracy of diagnosis. The disadvantage is that the procedure is

invasive and costly and requires expertise to perform. Its sensitivity is affected in individuals taking anti-secretory therapy.

RAPID UREASE TEST

Also known as “CLO Test”. Endoscopy is performed and biopsies are taken. Samples are placed on reaction strip or agar gel containing Urea, Buffer and a pH indicator. The Urease present in the bacteria will breakdown the urea impregnated and will release ammonia that will cause the pH indicator to change colour. This indicates positive result. It is inexpensive and results have to be read within 3 hours.Anti-secretory and antibiotic therapy will cause false negatives. Hence it is not recommended for those on therapy.

CULTURE

Culture is not routinely performed. It is useful only in cases of treatment failure to assess sensitivity and plan further treatment.

Specific conditions required are

- 5 to 7 days if culture plates are held at 37 degrees Celsius
- 5 – 10% oxygen and 5-12% carbon dioxide with humidity
- Brucella agar with 5% horse blood
- Brain Heart infusion agar enriched using 7% horse blood – Most successful

- Other media used include Chocolate agar, Mueller-Hinton agar, Wilkins Chalgren media.

  Colonies will be Urease , oxidase and catalase positive and Hippurate negative. The later will distinguish H.pylori from other enteric organisms.

Non adherence to strict culture conditions will show grey translucent colonies with swarming.

The reasons for negative culture may be as follows

- Only one biopsy from each patient. Increasing the number of specimen from a single patient will improve the yield from the culture
- Helicobacter is a slow-growing , fastidious organism and may not properly culture if conditions are not met.
- Patient ingestion of anti secretory drugs can reduce viability of bacteria
- Use of abundant gluteraldehyde solution to sterilize the endoscope may have deleterious effect on the organism.

FECAL ANTIGEN TEST

This utilizes Enzyme immunoassay format. It uses multiple monoclonal antibodies to detect H.pylori. It is more accurate than serology in population with low pretest probability. Therapy caused altered results. Fecal

antigen testing can be used 4 weeks after completion of therapy to assess effectiveness. It is an alternate to Urease Breath Test for this purpose.

There are numerous other methods of diagnosis, though most are only of research value rather than actual diagnostic value. One such method is isolation from Dental plaques. Their presence in dental plaques can be explained by the fact that the area around the plaques has low redox potential and hence promotes the growth of facultative anaerobes. The bacteria normally present ferment carbohydrates in the food thereby producing low pH levels. This microaerophilic anaerobic environment is ideal for growth of Helicobacter pylori with the average oral temperature of 35 – 37 degrees Celsius.

Blood testing and Breath test are often the first line investigatory modalities in common usage

There are numerous modes of testing for Helicobacter pylori but none are foolproof.

For Example, The urine ELISA which is not commonly used has a sensitivity of 96% and specificity of 79%.

The most reliable methods are

- Endoscopic Biopsy and Rapid Urease Test
- Histological Examination
- Microbial Culture

Cure of the disease can be confirmed by

- Urease Breath Test
- Fecal Antigen Test

They should be performed after 4 weeks of completing treatment. Serology is not useful to assess success. If they are positive, patient should be subjected to Endoscopy, biopsy and sensitivity testing.

CHOICE OF DETECTION METHODS BASED ON CLINICAL SITUATION

New Onset Peptic Ulcer

Patients diagnosed by radiograph or endoscopy should undergo Rapid Urease test or Serological Testing respectively. If found to be positive , the patient has to

undergo an eradication regimen. If initial tests show negative, the result has to be confirmed by another test.

If the confirmatory test is also negative, the patient is put on standard ulcer therapy with PPI or H2 Blockers.

If the confirmatory test is positive , then the initial test is taken to be false negative and treatment instituted with an effective H.pylori regimen.

History of Peptic Ulcer Disease

Patients who are on anti-secretory medications may have documented disease or self reported disease. All these cases should undergo non-invasive diagnostic testing.

If negative , anti-secretory therapy should be stopped. After 4 weeks of stoppage, the patient should undergo stool antigen or after 2 weeks should undergo Urease Breath Test.

If found to be positive, therapy must be given. If still negative, no role of anti-secretory or anti H pylori medications. Patients with objective evidence are more likely to have infection with Helicobacter.

Dyspepsia

Recent onset dyspepsia and younger than 50 years of age with no 'alarm'symptoms should undergo non-invasive testing. This may be Urease breath test or Serological testing. If found positive treatment is started.

In patients with age more than 50 years and alarm features, direct endoscopy is too be performed. If ulcer is found , biopsy and Rapid Urease Test is done and if positive , therapy started. If negative, then serological test or histological examination of the biopsy specimen is indicated.

TREATMENT OF HELICOBACTER PYLORI INFECTION

"Eradication" is defined as "Negative test for 4 weeks or longer after completion of therapy" . Suppression of the bacteria may occur during therapy and hence failure to detect the bacteria within 4 weeks of therapy may give false-negative results. The therapeutics of Helicobacter pylori infection involves 3 step approach – Diagnose , Treat , Confirm Cure. The very location of the bacteria provides unique challenges in the treatment of infection. The drugs used for treatment need to penetrate the thick gastric mucous and also need to be highly active in a very low pH environment. In 1990's monotherapy was advocated. However, emerging anti microbial resistance to single drug therapy led to the advent of multidrug combination anti microbial therapy.

According to the Maastricht 2-2000 Consensus Report[46] , eradication is strongly recommended in

- All patients ulcer disease
- In patients with low grade MALTomas
- In individuals with atrophic gastritis
- After gastric cancer resection
- First degree relatives of patients diagnosed with cancer stomach

The question of whether patients with functional dyspepsia, chronic NSAID therapy and individuals with GERD should be treated remains under debate. However, individuals with H.pylori positive non-ulcer dyspepsia and those with corpus-predominant gastritis should undergo eradication. These individuals are more susceptible to develop gastric adenocarcinoma than those with antral-predominant disease. Hence patients with non ulcer dyspepsia showing corpus-predominant gastritis should always undergo a regimen to eradicate infection.[47]

Eradication of Helicobacter pylori in chronic NSAID users has been shown to reduce the incidence of developing peptic ulcer.[48]

90-100% of duodenal ulcers heal within 8 weeks of anti-secretory therapy. Anti-secretory drugs donot change the natural history of the disease. They provide only symptomatic aid and delay the development of complications. Only the eradication of H.pylori can alter the natural history of the disease. Eradication decreased the incidence of ulcers and ulcer recurrence.[55] It also prevents rebleeding from ulcers and normalizes the histology and acid secretion in chronic gastritis.Earlier clinicians believed in 6 week therapy. However, current consensus suggests 2 weeks therapy is sufficient.

MARKOV MODEL

- All patients with dyspepsia were enrolled
- Patients should not have any alarm features like bleeding or weight loss
- Any patient tested positive for H.pylori received triple drug therapy
- If no relief or symptoms recur, patient should undergo endoscopy and biopsy.

  This model aims at reflecting the 'typical' approach to dyspepsia management.

DRUGS USED IN TREATMENT

The drugs currently used in the armamentarium against Helicobacter pylori are

- Proton Pump Inhibitors (PPI)
- Bismuth Salts
- Metronidazole
- Clarithromycin
- Amoxicillin
- Tetracyclines

PROTON PUMP INHIBITORS

PPI's have a direct anti-microbial effect against Helicobacter pylori invitro. However , in the invivo setting this effect seems to be of little actual value in eradication of infection.

Mechanism of action

Proton pump inhibitors act by irreversible inhibition of H^+/K^+ ATPase pump found in the acid secreting cells.This pump forms the final effector system and hence is the best target to be knocked off.

The reason for PPI being much more effective than H_2 Blockers are

- Targeting the terminal step in acid production
- Irreversible inhibition of the H^+/ K^+ ATPase pump

They suppress acid secretion by up to 99%.

The elevated pH in the stomach will hasten the healing of duodenal ulcers. The drawback of this decrease in Hydrochloric acid is that the normal amount of HCl required for protein metabolism and Vitamin absorption is not available.

The proton pump inhibitors are given in an inactive form. This inactive form is lipophilic and easily crosses into parietal cell canaliculus that have acidic

environments. In an acid environment, the inactive drug is activated by a process known as protonation and is converted into its active form. It is this active form that will covalently and irreversibly bind to the gastric proton pump and cause inhibition.

Pharmacokinetics

The absorption and bioavailability are suppressed by concurrent food intake. However, there seems to be no proven reports of this phenomenon affecting the efficacy or bio-availability of the drug.

The $t_{1/2}$ of proton pump inhibitors is ½ to 2 hours but a statum dose can last for upto 3days as the drug is accumulated in the oxyntic cells and also recovery of H/K ATPase pump takes long time.[59]

These drugs

- Decrease gastric acidity and thus prevent degradation of the drugs in the stomach
- Decrease gastric juice volume
- Decrease washout of the drugs and enhances luminal antibiotic concentration

BISMUTH

Bismuth is one of the first agents used against H.pylori. It is directly bactericidal. Bismuth subsalicylate - chemical formula of $C_7H_5BiO_4$, is a colloidal substance. Its chemical structure is yet to be fully delineated. An empirical structure $Bi_{38}O_{44}\{C_6H_3(OH)CO_2\}_{26}$ has been recently put forth. Its Minimum Inhibitory Concentration (MIC) is high.

Mechanism of action

- Inflammed tissues are coated and it prevents exudation of fluid from them
- It promotes absorption of fluid secreted into the lumen
- Inhibition of synthesis of inflammatory mediators such as Prostaglandins
- Reduces gastric motility
- Buffering of bacterial toxins
- Direct bactericidal effect of salicylic acid
- 'Oligodynamic'Effect – Bismuth heavy metal in non-toxic doses has anti bacterial action
- Weak antacid properties

Children should not take medication with bismuth subsalicylate while recovering from influenza or chicken pox, as evidence points to an association

between the use of salicylate-containing drugs during active infection and convalescent period and the onset of Reye's syndrome. For the same reason, it is recommended that nursing mothers not use medication containing bismuth subsalicylate because small amounts of the medication are secreted in breast milk and pose a chance of Reye's syndrome to nursing children.[60]

METRONIDAZOLE

It is a very effective drug. It is actively secreted into the gastric juice and saliva. Its action is pH independent. It is ingested as a pro-drug that is activated by bacterial nitroreductase. The mechanism of action is it causes loss of helical structure of bacterial DNA, strand breakage and hence impairment of bacterial function.

Metronidazole, taken up by diffusion, is selectively absorbed by anaerobic bacteria and sensitive protozoa. Once taken up by anaerobes, it reacts non-enzymatically with reduced ferredoxin, which is generated by pyruvate oxido-reductase. Many of the reduced nitroso intermediates will form sulfinamides and thioether linkages with cysteine-bearing enzymes, thereby deactivating these critical enzymes. As many as 150 separate enzymes are affected.

Also, the Metronidazole metabolites are taken up into bacterial DNA, and form unstable molecules. This function only occurs when Metronidazole is

partially reduced, and because this reduction usually happens only in anaerobic cells, it has relatively little effect upon human cells or aerobic bacteria.[61]

Though there has been an increase in bacterial resistance, this can be overcome by increasing the dosage.

CLARITHROMYCIN

It is a macrolide antibiotic, a derivative of Erythromycin. However, the former is more acid-stable and has consistent absorption characteristics than the latter.

Mechanism of action

Clarithromycin binds to the subunit 50S of bacterial ribosome and inhibits the translation of peptides. Besides this bacteriostatic effect, clarithromycin also has bactericidal effect on certain strains. It has a longer elimination half life compared to Erythromycin. 90% of H.pylori eradication regimen use Clarithromycin.

Pharmacokinetics

Clarithromycin is acid resistant and hence orally consumable. It attains high concentration in phagocytes.This enables its transport to the site of infection. During active phagocytosis, large concentrations of clarithromycin are released, as much as 10 times than blood concentration. Peak concentrations were found in hepatocytes and lungs.

Metabolism

Clarithromycin shows rapid first-pass metabolism. However, 14-hydroxy Clarithromycin is twice as active and has a longer half-life of seven hours as against five hours for Clarithromycin. Elimination is primarily by urine and bile. It has the best bioavailability at 50%.

Side Effects

Its most common side effects are nausea, abdominal pain . Other side effects include irritability, headaches, rashes, parosmia, dysguesia including a metallic taste. Anxiety attacks and nightmares may be seen. More serious side effects are cirrhosis and acute renal failure. Chest pain, palpitations and rhythm disturbances have also been documented.

An interesting finding is that Clarithromycin causes positive results on urine drug screens for cocaine.It can very rarely cause organic psychosis.[62]

When taken along with some statins, myalgia may occur. A risk of oral candidiasis, due to the elimination of oral microbial flora is also known to occur.

Resistance

Resistance cannot be surmounted by increasing the dosage of the drug. Development of resistance is mostly through receipt of the *erm*(B) gene. This gene also causes development of resistance to all macrolide group of antibiotics.[63]

Contraindications

- Not to be used in Hepatic or Renal insufficiency
- Individuals with cardiac problems like arrhythmias[64]
- Pregnancy
- HIV patients as florid interaction with Retro viral drugs is documented
- Epileptics on Carbamazepine (CBZ) . Metabolism is inhibited leading to accumulation and extra-pyramidal side effects

AMOXICILLIN

It is related to Ampicillin. It is a Beta-Lactam antibiotic.

Mechanism of action

β-Lactam antibiotics are bactericidal, and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cellwall. The peptidoglycan layer is important

for cell wall structural integrity, especially in positive organisms, being the outermost and primary component of the wall. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin-binding proteins (PBPs). PBPs vary in their affinity for binding penicillin or other β-lactam antibiotics. The amount of PBPs varies among bacterial species.

The β-lactam nucleus of the drug irreversibly binds to Serine residue of the PBP active site. This prevents the final cross linking of the peptidoglycan and interferes with bacterial cellwall synthesis.[65]

This drug is efficacious but providing gastric anti-secretory co-therapy is required.

TETRACYCLINES

These are polycyclic naphthacenecarboxamides. They act at the bacterial ribosome and prevent protein synthesis leading to production of non-functional proteins. They enter into the bacteria by two mechanisms – Passive diffusion through outer membrane hydrophilic pores. The second process is by an energy-dependent active transport system that pumps the drug through the inner cytosolic membrane. Once inside the cell, they attach to 30s subunit of bacterial ribosome and prevent aminoacyl tRNA access to the acceptor sites causing premature chain termination.

Human cells do not contain 30s Ribosome subunits and hence these group of drugs do not affect normal human cells.

CANADIAN HELICOBACTER STUDY GROUP

TREATMENT RECOMMENDATION

- All Helicobacter positive patients with gastric or duodenal ulcers , whether symptomatic or asymptomatic, should receive eradication treatment.
- All H.pylori positive patients with MALToma must receive eradication treatment.

RECOMMENDED THERAPY

- Clarithromycin 500mg bd + Amoxicillin 1000mg bd + PPI bd for 7 days
- Clarithromycin 500mg bid + Metronidazole 500mg bid + PPI for 7 days

ENDORSED THERAPY

- Amoxicillin 1000mg bid + Metronidazole 500mg bid + PPI bid for 7 days
- Tetracycline 500mg qid + Metronidazole 250mg qid + Bismuth subsalicylate 2 qid for 14 days

FOR TREATMENT FAILURE WITH FIRST LINE METRONIDAZOLE

- Clarithromycin 500mg bid + Amoxicillin 1000mg bid + PPI bd for 7 -14 days
- PPI bid + Bismuth 2 q6h + Metronidazole 500mg q6h + Tetracycline 500mg q6h for 2 weeks

FOR TREATMENT FAILURE WITH AMOXICILLIN AS FIRST LINE

- Metronidazole 500mg bd + Clarithromycin 500mg bd + PPI bd for 2weeks
- Bismuth subsalicylate 2 q6h + Metronidazole 500mg bd + Tetracycline 500mg qid + PPI bid for 2weeks

REGIMEN CURRENTLY USED

- First line therapy - triple therapy using
    - **PPI bd + Clarithromycin 500mg bd + Amoxicillin 1g bd for 7 days.**
- Second line therapy includes quadruple therapy based on
    - **PPI + Bismuth salt qid + Metronidazole 500mg tds + Tetracycline 500mg qid for 2weeks**

Another second line therapy has been put forth which is claimed to be better than the standard quadruple therapy second line management

- **Rabeprazole 20mg bd + Amoxicillin 1000mg bd + Levofloxacin 500mg od for 10 days.**

Rescue regimen after failure of initial treatment extends for 14 days. It includes,

- **RIFABUTIN 150mg bd + LEVOFLOXACIN 500mg OD + AMOXICILLIN 1000mg bd + PPI bd for 14 days**

- **RIFABUTIN 150mg bd + Ciprofloxacin 500mg bd + Amoxicillin 1000mg bd + PPI bd**

- **Tetracycline 500mg qid + Furazolidone 200mg bd + Bismuth subcitrate 120mg qid + PPI bd**

The standard dose of PPI in all above regimen signifies the following dose twice a day

- Esomeprazole 40mg
- Omeprazole 20mg
- Lansaprazole 30mg
- Pantoprazole 40 mg
- Rabeprazole 20mg

OTHER REGIMEN

There are certain parallel concept on treatment of H.pylori. A few are discussed here.

- Sequential Therapy
    - **PPI + Amoxicillin followed by PPI + Clarithromycin + Metronidazole – 5 days course of each set**
- Concomitant Therapy
    - All 4 drugs are administered together. It is less complex
- Extended Sequential Therapy

  continued for 14 days i.e. 7 days plus 7 days instead of 5+5

- Sequential Concomitant Hybrid Therapy

  Extended Sequential Therapy + Continuing Amoxicillin for the entire 14 days duration.

- Under study

  Four times daily administration of three capsules containing

  420 mg Bismuth subcitrate + 375mg Metronidazole + 375mg Tetracycline and also 20mg Omeprazole twice daily for 10 days.

- In Metronidazole resistant H.pylori , the following regimen shows >92% success rate.
  - **Tetracycline 500mg qid + Metronidazole 500mg tds + Omeprazole 20mg bid + Bismuth subsalicylate 2 tablets qid**
- A newer 4 drug regimen for H.pylori eradication is under trial in Western countries. These are the LOAD and LAC regimen

LOAD Regimen

Levofloxacin 250mg in the morning

Omeprazole 40mg on an empty stomach

Nitazoxanide 500mg bd with food

Doxycycline 100mg at night

LAC Regimen

Lansaprazole 30mg before breakfast

Amoxicillin 1000mg bd with meals

Clarithromycin 500mg bd with meals

SIDE EFFECTS OF DRUGS

PPIs	Headache, Diarrhoea
Clarithromycin	GI upset, Diarrhoea, Dysgeusia
Amoxicillin	GI upset, Diarrhoea, Headache
Metronidazole	Metallic taste, Dyspepsia, Disulfiram like reaction
Tetracycline	GI upset, Photosensitivity
Bismuth subcitrate	Darkening of tongue and stools
Furazolidone	Nausea, Headache, Malaise, Hypersensitivity, Hemolytic anemia, disulfiram like reaction
Rifabutin	Red discolouration of urine, Rash, Diarrhoea, Vomiting, Ocular and Myelotoxicity
Levofloxacin	QT Prolongation, Seizures, Glucose intolerance

KEY ASPECTS

An "optimal therapeutic regimen" should produce >95% success rate in patients infected with susceptible strains. In cases infected with strains that are resistant , a cure rate of >85% is necessary.

The logic behind twice daily administration of PPI is that the use of bismuth alone or once daily dose of PPI raises intragastric pH to around 4 – 5. This causes many bacteria to remain quiescent. For more effective eradication , more profound elevation of pH is essential . Hence bid dose of PPI is much more quintessential to eradication. However, in countries like Japan, where the people metabolize PPI slowly, there remains a prolonged effect even after once daily administration. Eradication can be achieved even by dual therapy with Amoxicillin and PPI.[58]

- An adequate strategy is to apply two therapies to ensure 100% cure
- Repeating the same course is not recommended
- First choice should never include both Clarithromycin and Metronidazole
- If PPI are not tolerated, they can be replaced by H2 Blockers
- Use of Rabeprazole may be beneficial compared to Omeprazole because of heterogeneity in enzymatic activity[73]

- Nonspecific drug reactions are liable to be misplaced as penicillin allergy. Hence investigation to rule out are essential. Patient should not be deprived of the effective penicillin therapy
- Prolonged treatment for 2 weeks is ideal
- Assessment of antibiotic sensitivity is needed to prevent resistance

Though combining Clarithromycin and Metronidazole is highly effective, the problem occurs in cases of treatment failure. The bacteria will develop double resistance against both agents and further empirical therapy and regimen selection would become impossible.[50]

ANTIMICROBIAL RESISTANCE

Resistance can be primary – prior to initiation of therapy or secondary following failure of therapy. Resistance to Tetracycline and Amoxicillin are extremely rare.[51] The prime concern is with resistance to nitroimidazole groups like Metronidazole and macrolides like Clarithromycin. An interesting observation is that increasing the dose of Metronidazole from 1.0 to 1.5 mg/kg overcomes this resistance. However , Clarithromycin enjoys no such benefit. Resistance once formed leads to complete loss of effect irrespective of dosage.

TREATMENT FAILURE

Anti-microbial therapy often fails to eradicate the bacteria because of presence in certain sanctuary sites. This includes the oral cavity. The drugs act only at the level of stomach. The mechanism by which the organism harbours at the sanctuary sites still remains to be debated. However, one possible explanation would be that the bacteria is refluxed up from the stomach and gets lodged in dental plaques, which form the normal oral biofilm of the host.[54]

FOLLOW UP

Duodenal ulcers recur in only 6 % of cured patients in contrast to 67% in positive cases.

Gastric ulcers recur in only 4% as against 59% in positive cases. Relief of symptoms alone cannot be taken as a sign of cure. Persistence of ulcer related symptoms may indicate persistence of infection. [66,67] However, continued symptoms too does not always indicate treatment failure. Therefore , follow-up with a confirmatory test to evaluate eradication of Helicobacter, irrespective of presence or absence of dyspeptic symptoms is always necessary. Non-Endoscopic testing is preferred if confirmation is sought.

Serology is not useful in the immediate post-treatment period due to high titre of antibodies in circulation. [68] After more than a year , seroconversion can be taken as a reliable confirmatory indicator of eradication. [69]

PERSISTANT INFECTION AFTER TREATMENT

- Patient compliance to eradication therapy has to be assessed
- Confirmation to presence of infection must be sought by either a non-invasive test preferably, or by invasive modalities.
- If found positive, second line eradication therapy has to be given
- If persistent even after second line management, antibiotic susceptibility has to be assessed and appropriate drugs given.

DISCUSSION

Numerous studies have been a forerunner to ours in elucidating various aspects of disease caused by Helicobacter pylori infection. Each one has analysed particular aspects of the natural history of the infection and given varying conclusions.

Javed et al. in 2010 have demonstrated an overall prevalence of around 80% in Peptic ulcer patients . They have also reported that epigastric pain being the most common symptom. The same study group has also showed maximum prevalence of infection in the age group of 48 years to 55 years. Similarly, Sasoon Levi et al. in 1989 have demonstrated a prevalence of 86.27% and Querseshi et al. in 1997 have shown 92% prevalence.[76] Our present study has shown similar results with the prevalence being perched at around 87.8%.

Gisbert at al, have demonstrated a prevalence of 60% in perforated peptic ulcers as against close to 90% in uncomplicated peptic ulcer disease. [79] Both the above statistical observations are consistent with the figures derived from this study also.

Obata et al. have evaluated the diagnostic accuracy of serological tests against the ‘gold standard’ tests and have reported sensitivity in the range of 87.5%

to 95.5% and specificity in the range of 84.8% to 92.3%.[77] The kit used in this study carries with it values of sensitivity 95.1% and specificity 94.1%.

One of the commonly used test for Helicobacter pylori in the Urease Breath Test(UBT) . According to Miwa et al. UBT has sensitivity of 96·7% and specificity of 96.5%. [78] The serological kits used in our study has shown to carry comparable results.

Thijs JC et al.[80] have conducted a multi-center comparative study on various tests used to detect Helicobacter pylori. The observations from this study are as follows.

TEST	**SENSITIVITY**	**SPECIFICITY**
Culture	98.4	100
PCR	96.7	100
Microscopy	96	98.8
Rapid Urease	90.2	100
Urease Breath Test	100	100
Serology	98.4	88.4
Our Study	95.1	94.1

Helicobacter pylori is a omnipresent bacteria that has been linked to numerous gastrointestinal diseases which include duodenal ulcer, gastric ulcer, gastric cancer, MALT Lymphoma, Non Ulcer dyspepsia and other Extra Gastrointestinal diseases like Idiopathic Thrombocytopenic Purpura etc. Half a million people die around the world from Gastric cancer making it the third largest killer of human beings.Inspite of the well elucidated ill effects of the bacteria , there are numerous opponents that argue against the case of eradication of Helicobacter pylori.

The relationship between H.pylori infection and human host is proving to be complex. Risk posed by infection may involve differences in host susceptibility and virulence of the infecting strain.The strongest indication for eradication is duodenal ulcer . Marshall et al. has shown healing rates of upto 92% in treatment group and a much lower 12 month relapse rate.[44] Also in cases of Non-Ulcer dyspepsia, eradication provided symptomatic relief in upto 81% of cases and relief lasts for 12 weeks.[45]

The opponents of eradication argue that the environment in India is contaminated and GI infections are very common. Secondly, the widespread misuse of antibiotics has lead to widespread drug resistance. In numerous fixed dose combinations available in India, most have a sub-optimal dose of Amoxicillin. It is believed that the reinfection rate in India is around 60%.

Helicobacter pylori is an organism well adept to humans with persistent infection and low level disease. This behavior tends to point to the speculation that Helicobacter pylori is a commensal rather than a pathogen. It is highly likely that most in the community have avirulent strains of the bacteria that do not actually warrant eradication measures but also increases the possibility that eradication of such strains could be detrimental to health by abolishing H pylori induced gastric hyperacidity, destroying the natural barrier and leading to Gastrointestinal infections. Also it is believed to be a part of the body's own innate immune system. H.pylori infection may even prevent allergic and autoimmune diseases in humans.

The precise relationship between H.pylori and complicated ulcer remains to be established beyond doubt. Recurrent ulcers after peptic ulcer perforation occurs mainly in H.pylori positive individuals. All patients with perforated peptic ulcer should undergo simple closure of perforation followed by eradication of the bacteria. Disappearance of the organism prevents, or atleast decreases ulcer recurrence and ulcer perforation in the future. Therapy has to be ideally started in the immediate post-operative period. In current context, the only indication for elective definitive surgical treatment for peptic ulcer disease is patients with intractable symptoms even after adequate eradication attempts , who are H.pylori negative.

It has been shown that curing H.pylori infection may provoke reflux oesophagitis. It has been suggested that H.pylori infection enhances the ability of PPI's to suppress gastric acidity. Therefore H.pylori positive oesophagitis patients heal faster than those who are negative. Rebound hyperacidity occurs in H.pylori negative patients on stopping PPIs.[49]

The fact that though India has a much higher prevalence of H.pylori infection , there is a relatively lower risk of Gastric carcinoma. This paradox can be explained by the presence or absence of the more biologically active variant of CagA. The presence of less active form of the gene could explain the negligible incidence of gastric carcinoma in India.

Coming to the Serological testing aspects of Helicobacter pylori, several studies have shown that kits made in the Western countries have a far less diagnostic accuracy than those manufactured in the East. The Use of local antigen in manufacture of serology kits aids to improve the accuracy of results specific to that population.[70]

The identification of Helicobacter pylori infection in children with chronic abdominal pain is essential. However, the apt diagnostic method to be used is still under debate. Clearly it carries no advantage in subjecting children to invasive testing. However , use of serological testing in children needs to be validated.

Results are not reliable in the pediatric age group. An possible explanation to this paradox is that the child's immune response varies greatly compared to that of the adult population. The second explanation would be the lack of standardization and validation of commercially available assays with serum samples from infected and uninfected pediatric cases.[71]

Furthermore, the detection of IgG antibodies in the saliva and Urease Breath Test in children need to be performed and substantially validated. [72]

In adults, serological testing has got comparable results with other means such as ELISA. The higher the antibody titre, stronger will be the band that appears in Test line. If a faint band is considered seronegative, it decreases sensitivity whereas increases the specificity. Screening of dyspeptic individuals with serology prior to endoscopy reduces the endoscopy workload by almost 23.3% and only 3% of ulcers would be missed by doing so.[74]

Smoking has been proven as a major risk factor in modulating individual susceptibility to infection with Helicobacter pylori. Cessation of smoking prevents progression of disease. The prevalence of virulent strains of H.pylori is more among smokers than non-smokers. Smoking causes increased expression of cag genes. This predisposes to higher chances of malignant transformation of gastric mucosal cells.[75]

As no major improvements have come since the advent of the original antibiotics against H.pylori, it still remains that only optimization of therapeutic regimens may be useful at present. Probiotics may exert a favourable effect during therapy. Also , addition of bovine lactoferrin has been shown to increase efficacy. But human recombinant lactoferrin has not shown to offer any such advantage.[52]

There are numerous studies underway to explore the possibility of preventing Helicobacter pylori infection. The need for prevention arises from the rapidly growing antimicrobial resistance to the drugs used in treatment. Extensive vaccine studies have proven successful in mouse. [40] A number of foods are also believed to prevent infection. These include Green Tea, Red Wine, Broccoli sprouts, Garlic, Flavanoids and probiotics.[41] Supplementing food with Lactobacillus containing or Bifidobacter containing yoghurt improves rate of eradication.[42] Broccoli sprouts have a substance known as sulphoraphane that inhibits the bacteria.[43]

The isolation of Helicobacter from dental plaques is a well known entity but whether the removal of plaques causes any change in recurrence rate still remains under study. Due to limited availability of effective drugs, the ideal modus to treat would be to establish sensitivity prior to initiating treatment. The major obstacle to this is the invasive nature and cost factors prima facia involved in Upper GI Endoscopy and biopsy. Precise identification of virulent strains of H.pylori and

aggressive targeted eradication of only the virulent strains seems to be the optimum path to undertake. The possibility of the bacteria finding sanctuary in oral cavity and possibly causing recurrence needs to be explored and controlled. Eradication of Helicobacter present in the oral cavity requires precise identification of the oral bacterial ecological niche. Future developments in polymerase chain reaction and serology testing to detect Helicobacter pylori will aid in providing insight into oral H.pylori and open further possibilities for non-invasive testing and steps to prevent recurrence.

Helicobacter pylori is believed to be associated with other systemic and auto-immune diseases. To list out a few would be

- Chronic Urticaria
- Rosacea
- Psoriasis
- Sjogren Syndrome
- Henoch Schonlein Purpura
- Alopecia Areata
- Systemic Sclerosis
- Atopic Dermatitis
- Behcet Disease

- Generalized pruritus
- Immune Thrombocytopenic Purpura
- Lichen Planus
- Aphthous Ulcers
- Cholangiocarcinoma
- Hepatocellular Carcinoma
- Gallstone formation
- Inflammatory Bowel Disease
- Sideropenic Anemia

Helicobacter pylori increases permeability of stomach lining and thus increases exposure to allergens in the gastro-intestinal tract. This is a plausible explanation for association with Urticaria, Atopic Dermatitis and Generalized Pruritus. Also, there seems to be increased levels of nitric oxide in the blood leading to flushing and erythema of Rosacea. It triggers autoimmune reactions in skin and glands causing Sjogren Syndrome and Psoriasis.

In 1994, The International Agency for research on Cancer classified Helicobacter pylori as a ‘Carcinogen’. The risk of non-cardia gastric cancer is 6-8

folds higher in H.pylori infected individuals than those who are uninfected. Eradication leads to a moderate decrease in the risk of gastric cancers and also less worsening of pre-cancerous lesions. The organism is also linked to a rare type of Non-Hodgkin's B cell type Lymphoma arising from Mucosa Associated Lymphoid tissue called as MALT Lymphoma or simply MALTOMA. The stomach lining in reality lacks lymphoid tissue. It is because of the chronic inflammation produced by the Helicobacter that stomach acquires lymphoid tissue and MALTOMA arises from such tissue.

There seems to be an inverse relation between Helicobacter pylori and gastric cardia cancer. In the West, the effective eradication of H.pylori has paralleled the increases incidence of cardia cancers. This may be due to the decreases acidity in the stomach secondary to chronic gastritis leading to atrophy of the gastric glands. This causes reduced reflux into the esophagus .

Inspite of high incidence of infection in the Indian population, there seems to be a surprisingly low occurrence of sequlae of infection such as gastric adenocarcinoma.. Biological co-ordinates of such 'protection' needs to be studied with the aid of genome sequence of the bacteria. This type of research is feasible in the not too distant future as genomic study is becoming far and more affordable as years go by. The most widespread debate about this organism is whether it is a parasite, commensal or mutualist. There are certain evidences showing the bacteria

to be preventive in cases of mainly childhood enteric infections such as diarrhea and also in cases of GERD , Esophageal cancer and Asthma. Eradication of the bacteria can lead to increased occurrence of such diseases. In this context, Helicobacter pylori , with its aggressive eradication drive in the west can be classified as an 'endangered species'. It is considered that per-historic versions of the bacteria may be considered as 'human parasites' prior to acquiring virulence factors. The present day Helicobacter can be dubbed as a 'Commensal' only after its 'disarmament' meaning its virulence mechanism makes it a 'classical pathogen' .

H.pylori has also been proposed to have strong association with pancreatic and colorectal cancers. But this association is yet to be proven with accuracy.

An issue of paramount importance that has to be considered is the long term use of PPI for dyspepsia without screening and eradication of H.pylori can cause the following setbacks.

- Prolonged use of PPI causes persistent hypergastrinemia due to G cell hyperplasia, which may cause Gastric Carcinoid.

- Long term use alters the acid milieu of the antrum, which is the natural habitat of H.pylori, leading to migration of the bacteria more proximally to the fundus. This produces chronic fundic inflammation and intestinal metaplasia which has shown to cause fundic adenocarcinoma. Hence simple PPI therapy without H.pylori eradication , as commonly followed in clinical practice , can be detrimental or even dangerous to the patient.
- PPI abolish the symptoms and hence patient compliance with a full course of H.pylori eradication therapy comes under duress.

The widespread eradication of Helicobacter depends largely on the prevention of person to person transmission. Development of a prophylactic vaccine would open new avenues in the epic of Helicobacter pylori as a human pathogen from time immemorial. Finally, it is to be proved whether total eradication of this co-evolved pathogen is an absolute necessity or could prove detrimental in certain situations.

COST OF THERAPY

Vakil et al. after analyzing the cost effectiveness of various diagnostic modalities available for H.pylori concluded that the antibody testing incurred the lowest cost per correct diagnosis at all levels of prevalence compared to all other methods.[53]

The argument of whether first to go for endoscopy in symptomatic cases or to go for empirical therapy followed by endoscopy if necessary in persistent cases still remains under question. Though the Markov Model clearly shows endoscopy as the second step, this fact remains in a developing country such as ours that Empirical therapy be started first. This is mainly due to the cost factors involved with Upper GI endoscopy.

The cost of various anti-H.pylori kits available in the Indian market are as follows

ULCIKIT	Rs.26.00	Abbott India
OMOXITIN	Rs.13.84	USV Corvette
LANSIKIT	Rs.14.95	Zydus Cadilla
OMEPRAZ HP KIT	Rs.122.00	Alkem Labs
HELIKIT	Rs.24.16	Zydus Cadilla
HELIPAC KIT	Rs.25.00	Profic Organic
OMEPRAN HP KIT	Rs.25.00	Alkem Labs
LOKIT	Rs.27.50	Kopran Labs
HP KIT	Rs.33.00	Sun Pharma
ZOVANTA KIT	Rs.36.00	Dr.Reddy's Lab
PYLOMOX KIT	Rs.37.00	Ranbaxy Labs
OTC HP KIT	Rs.49.50	Biochem Pharma

LTC KIT	Rs.60.00	Ind Swift
HELIGO KIT	Rs.63.25	Intas Pharma
L-COT KIT	Rs.55.36	Lupin Pharma

Of all the drugs used in eradication of Helicobacter pylori, the drug Clarithromycin is the most expensive one. Its price for a single tablet varies from Rs.34 to Rs.69.

ALEMBIC	Rs.34.20
GLENMARK	Rs.55.00
ABBOTT INDIA	Rs.56.30
ZYDUS CADILLA	Rs.68.75
GLAXO	Rs.69.20
NOVARTIS	Rs.34.00

Though the drug Clarithromycin is highly effective against H.pylori, its exuberant cost limits its use in a country like our India.

CONCLUSION

Helicobacter pylori is one of the most successful colonizers of the human stomach of almost half the world's population. But only a small fraction of individuals develop H.pylori associated diseases.

From this study , the conclusions that can be drawn are as follows

- Non –Invasive testing by serology is a sensitive and specific modality of testing for mass screening purposes. This is because of its good performance characteristics and technical simplicity.
- Culture , microscopy and Rapid Urease Tests are the 'gold standard' in diagnosing H.pylori infection
- Patients with endoscopically proven peptic ulcers have a 87.8% positivity in H.pylori serology testing.
- Among acute presentation of perforative peritonitis, upto 59.5% are H.pylori positive.
- 60% of Distal Gastric Carcinoma are seropositive.
- Among those with Non-Ulcer dyspepsia, only 22% were positive.
- Treatment of Helicobacter pylori should be initiated at the earliest in positive cases. Eradication drastically reduces the recurrence of ulcers.

- Symptomatic management of gastritis with PPI alone without evaluation and eradication of H.pylori leads to proximal migration of the organism and proximal gastric cancers increase in incidence.
- It is always best to start with a regimen which has either Amoxicillin or Clarithromycin but never both in the same course. This prevents development of double resistance.
- 2 weeks therapy is far better than 1 week course.
- Eradication should be assessed 4 to 6 week after completion of therapy.
- Serology is not the ideal test to evaluate eradication. Eradication is to be proven by Urease Breath Test , Rapid Urease Test or by Stool Antigen assay.
- Persistent infection heralds resistance and requires susceptibility testing and treatment with second line or other rescue regimen

Helicobacter pylori infection is an 'Ice Berg' disease. The need of the hour is a well-targeted monotherapy that has least chance of leading to anti-microbial resistance. Helicobacter pylori is one of the most extensively studied bacteria in the history of human evolution and microbiology and yet it still remains the most difficult to comprehend and interpret. The Basic question of whether Helicobacter is a friend or foe still remains to be answered.

CHART 1 :

SYMPTOMATOLOGY

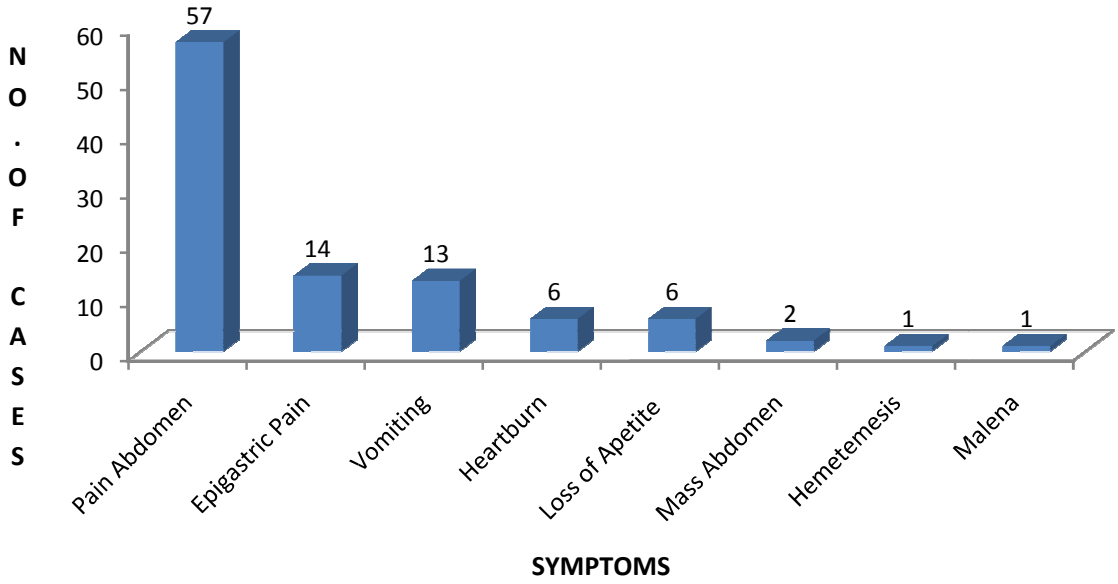


CHART 2 :

DURATION OF SYMPTOMS

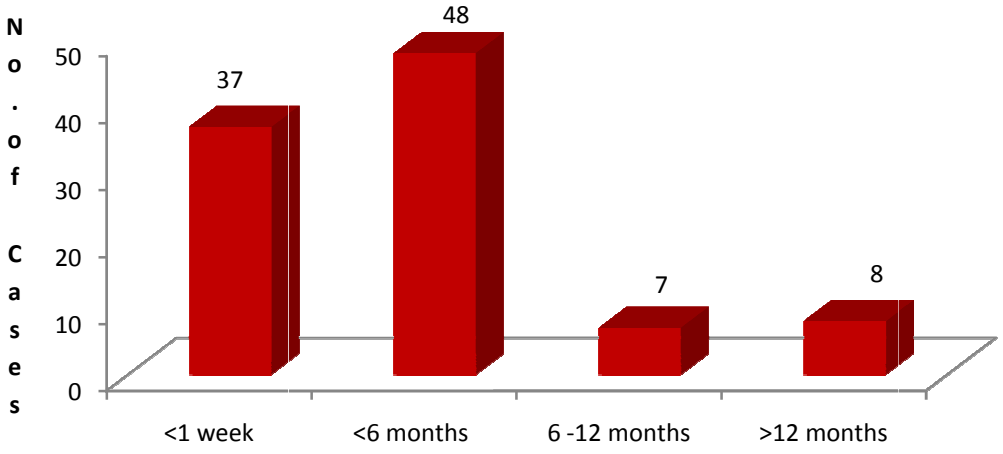


CHART 3

SEROLOGY IN SYMPTOMATIC CASES

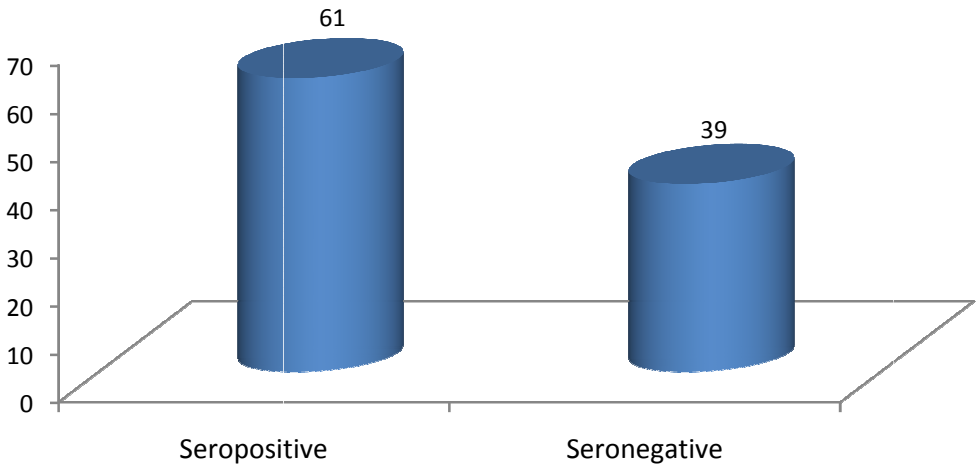


CHART 4

SEX DISTRIBUTION OF POSITIVE CASES

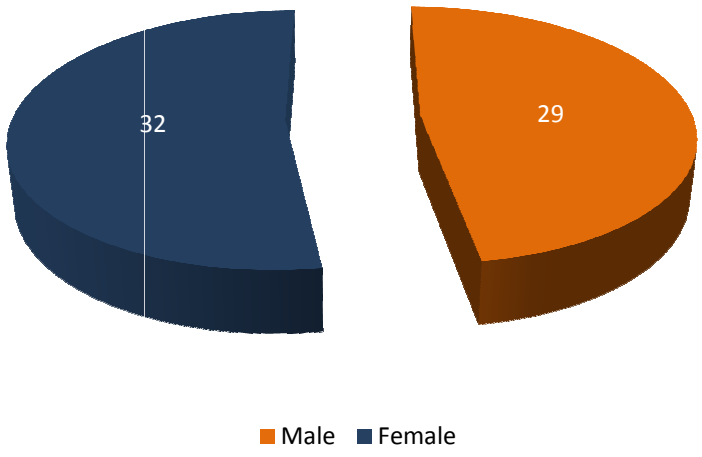


CHART 5

AGE DISTRIBUTION OF POSITIVE CASES

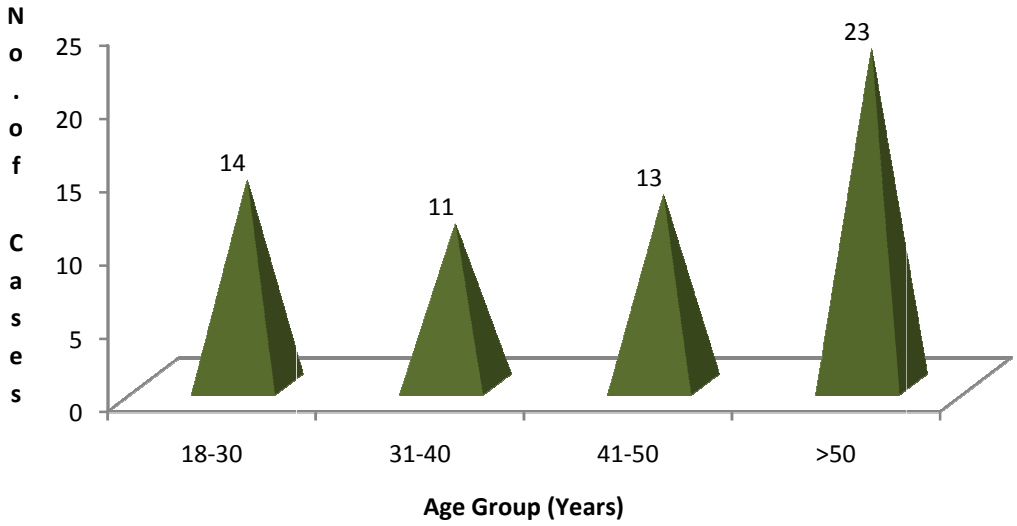


CHART 6

OVER THE COUNTER DRUG USERS

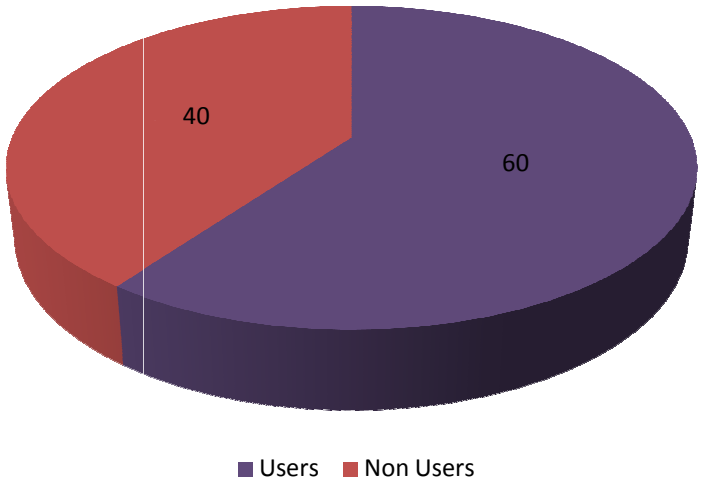


CHART 7

RISK FACTORS

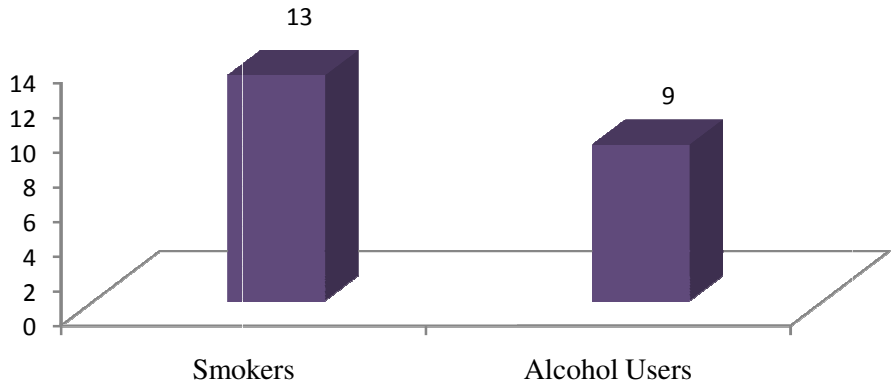
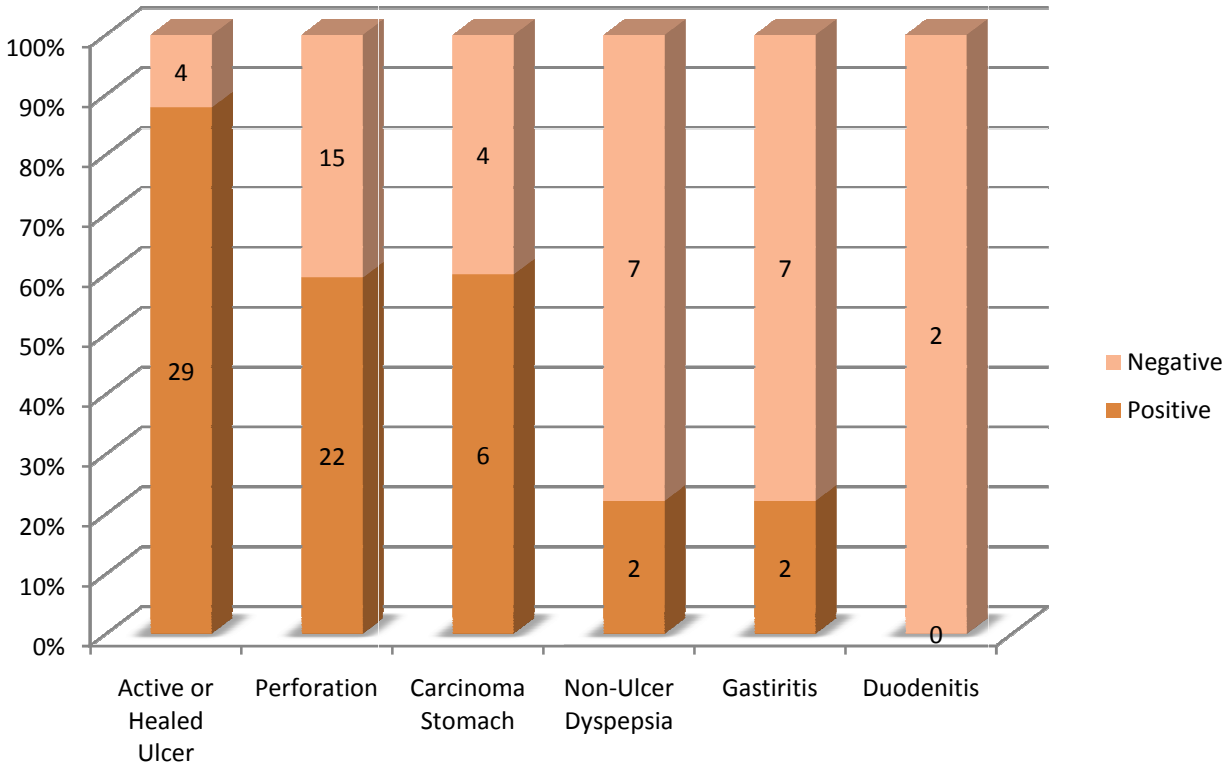


CHART 8

PREVALENCE OF HELICOBACTER PYLORI



PHOTOGRAPHS AND IMAGES

Fig 3 : Electron Micrographic picture of Helicobacter pylori

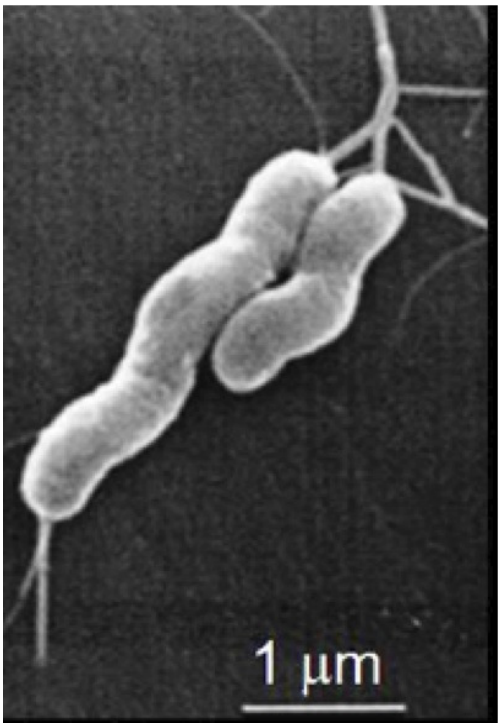


Fig 4 : Electron Micrographic picture of H.pylori adherent to gastric mucosa

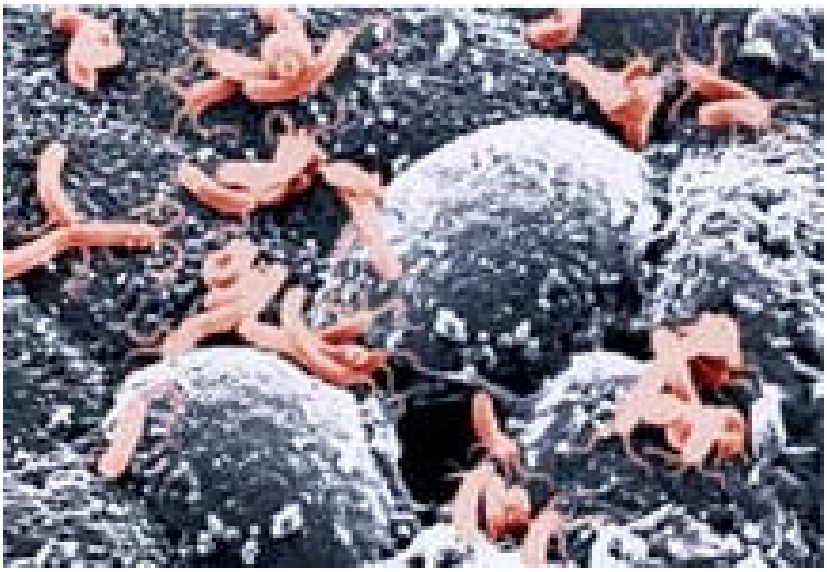


Fig 5 : Electron Micrograph showing dense colonization of antral mucosa

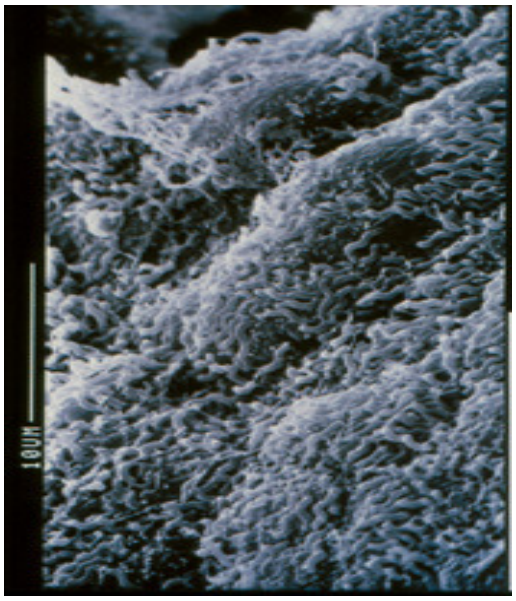


Fig 6 : Parts of the stomach

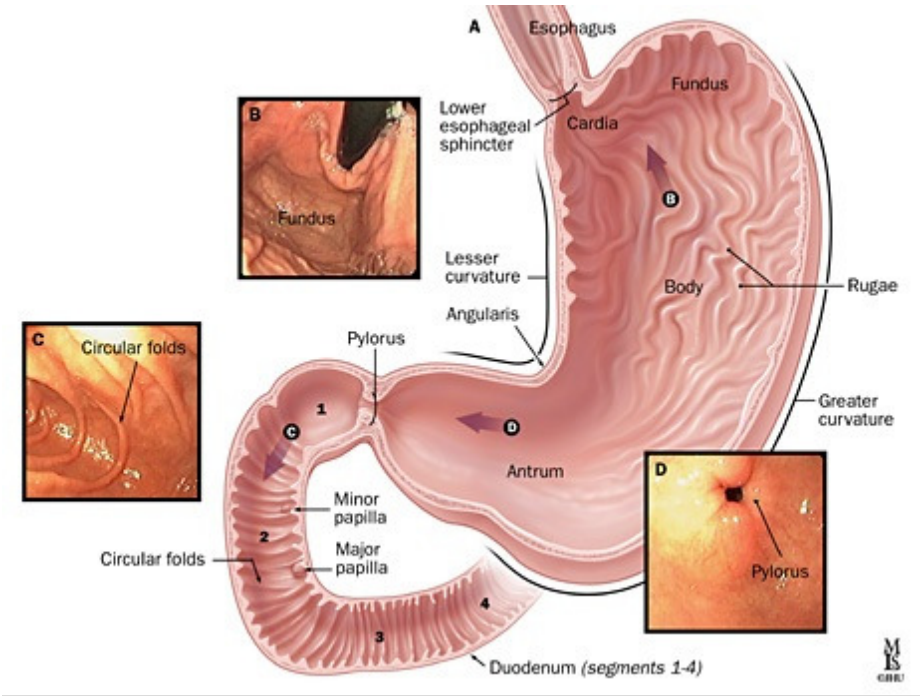


Fig 7 : Cross Section of Stomach Wall

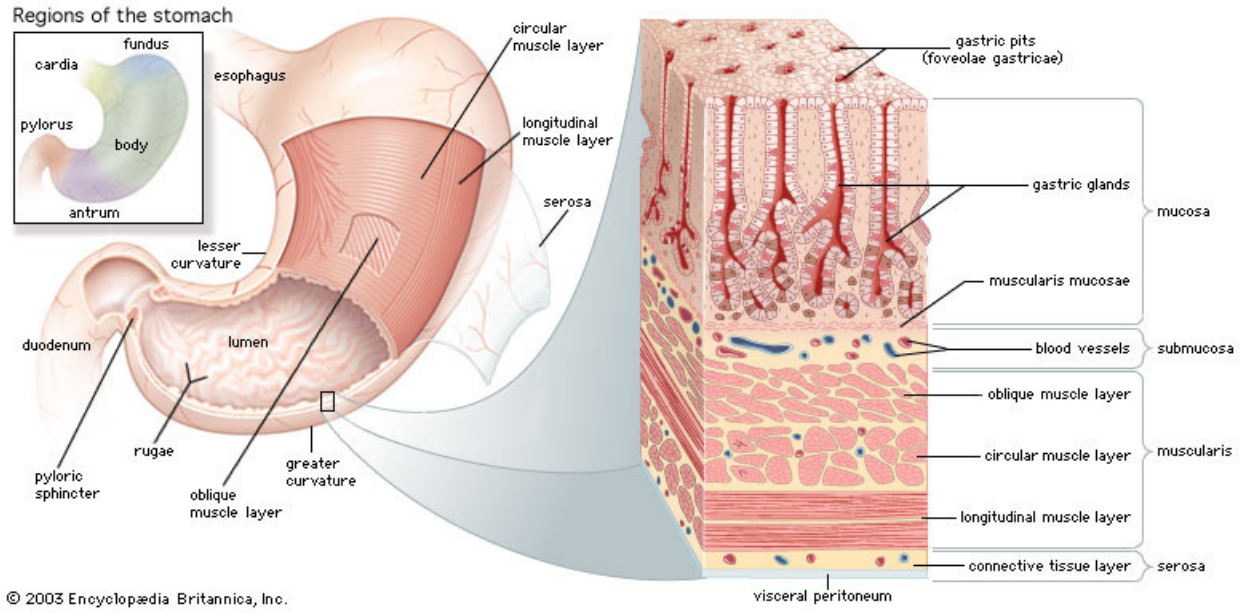


Fig 8 : Vasculature , Lymphatics and Innervation of the Stomach

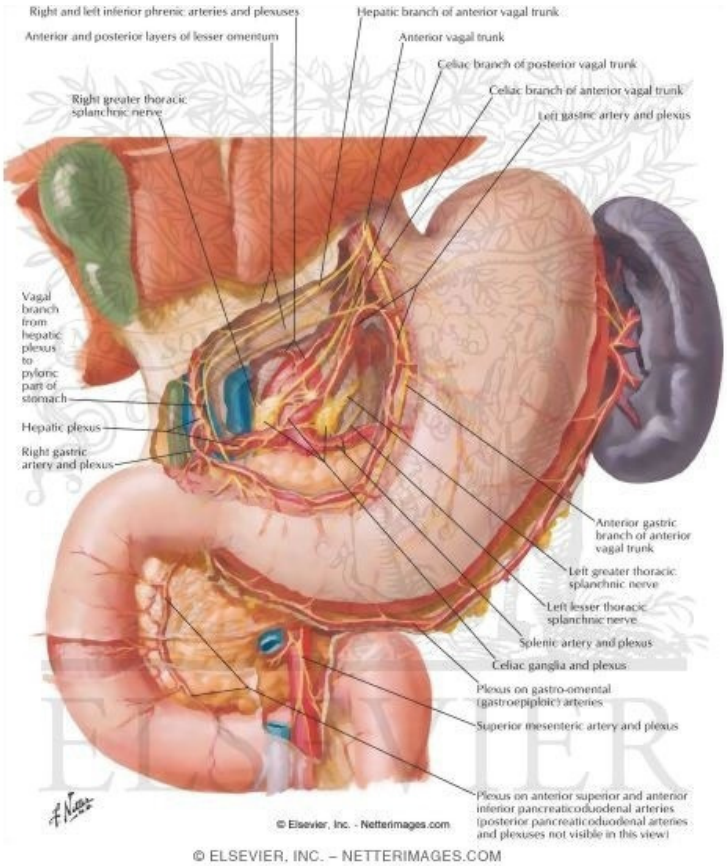


Fig 9 : Gastric Gland

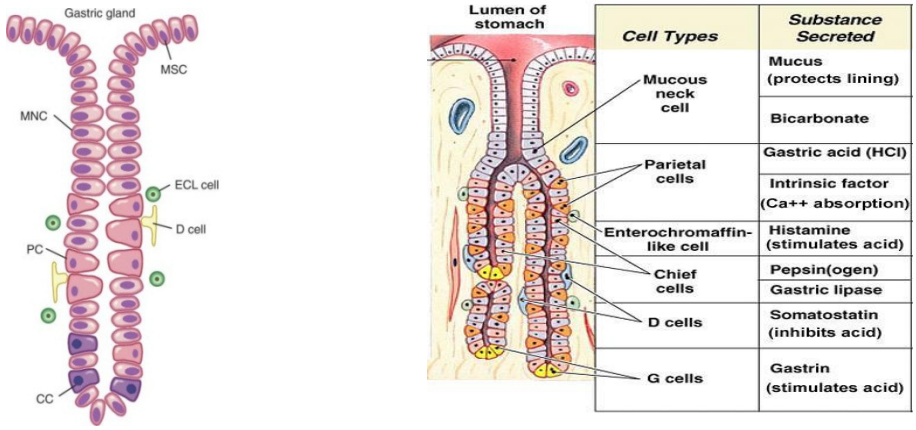


Fig 10 : Development of the Foregut

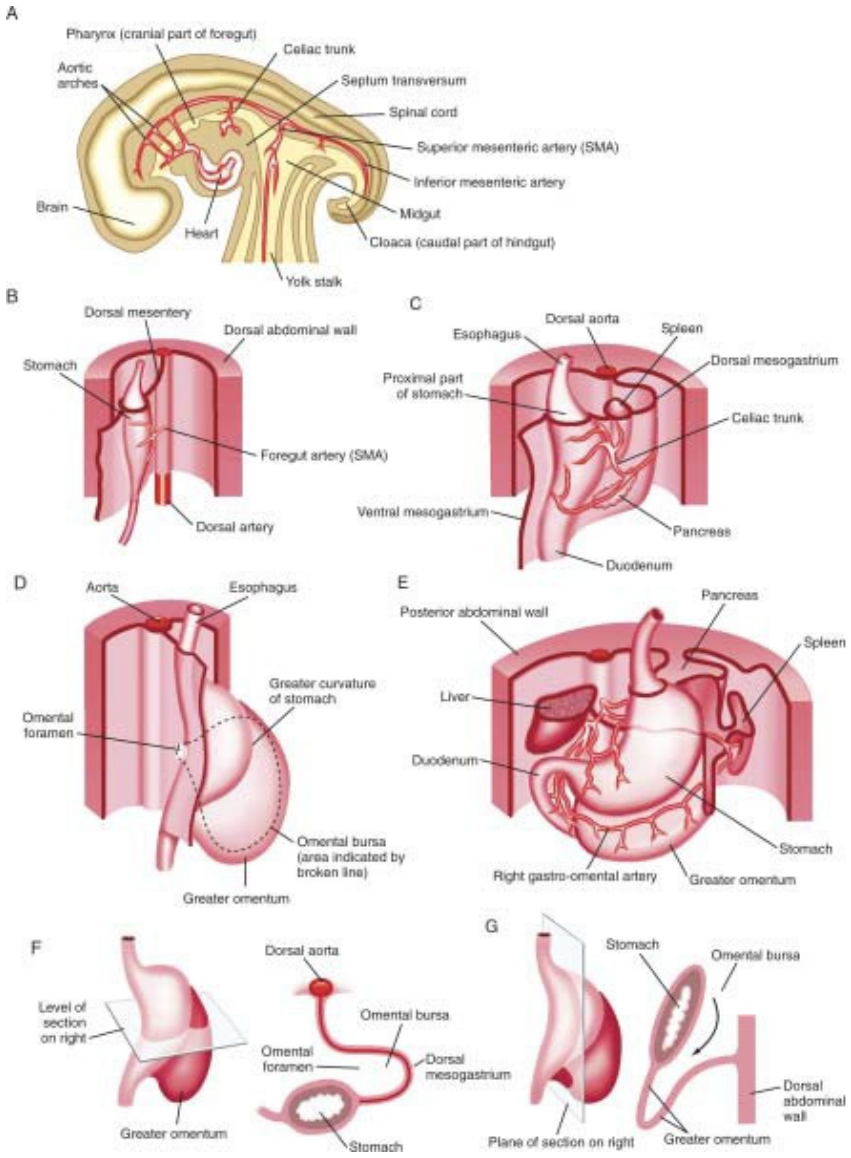


Fig 11 : H.pylori gastritis showing lymphocytic and Plasma cell infiltration

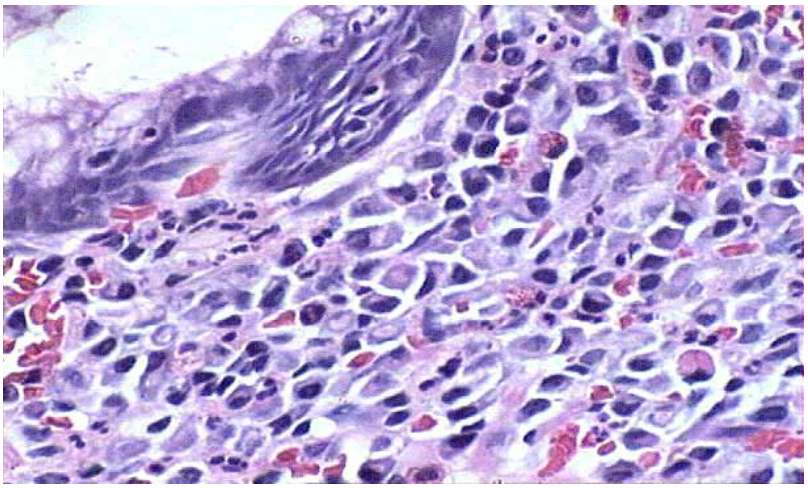


Fig 12 : Ulcer along the Lesser curvature

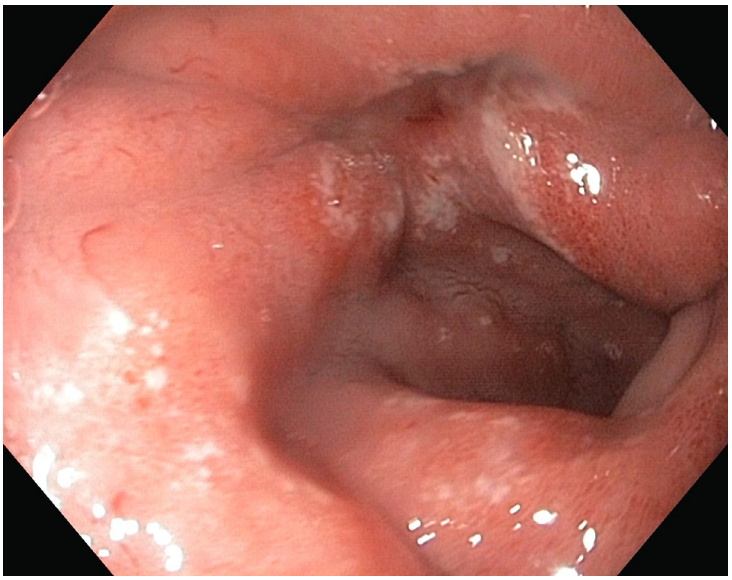


Fig 13 : Ulcer along the Greater Curvature

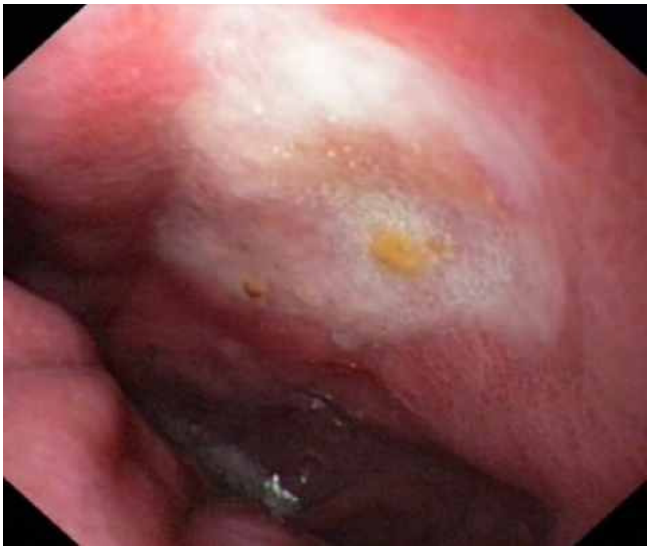


Fig 14 : Duodenal Ulcer

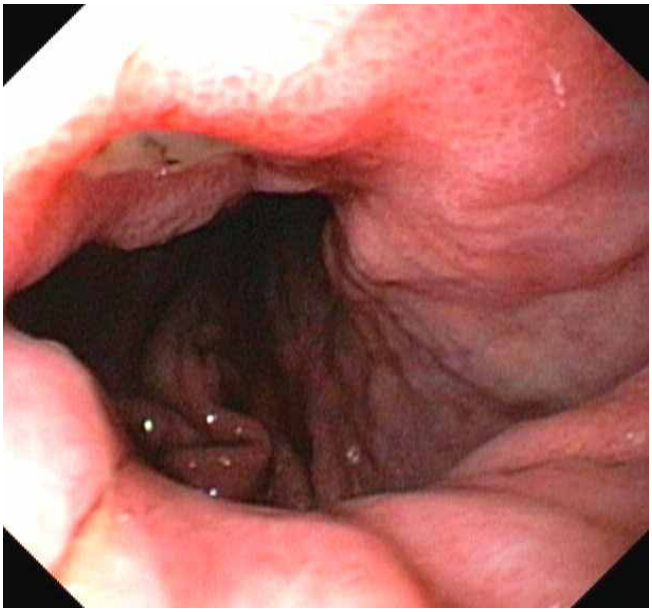


Fig 15 : Bleeding Duodenal Ulcer

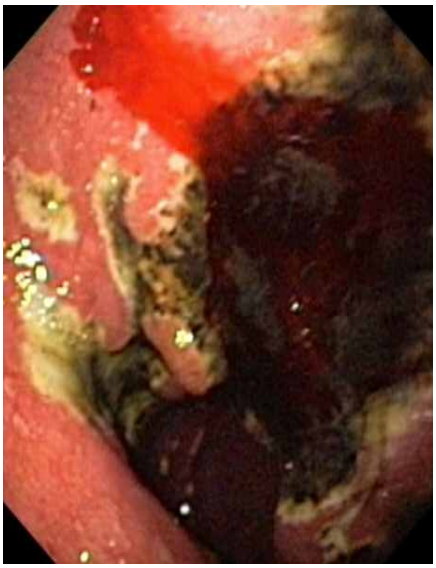


Fig 16 : Gastric Carcinoma

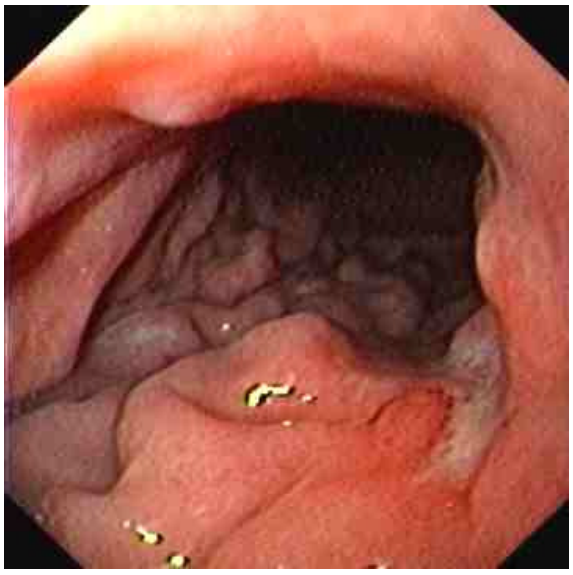


Fig 1 : Serology Card showing Positive result

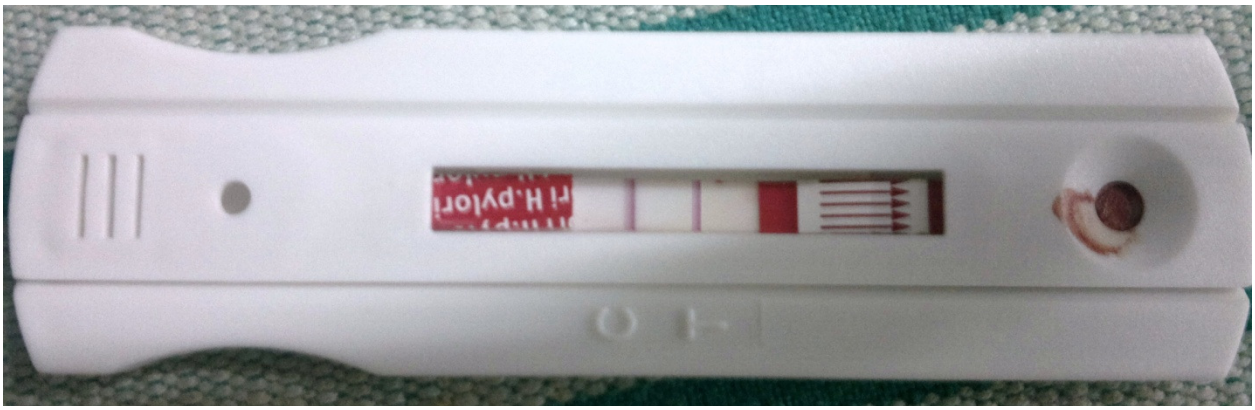
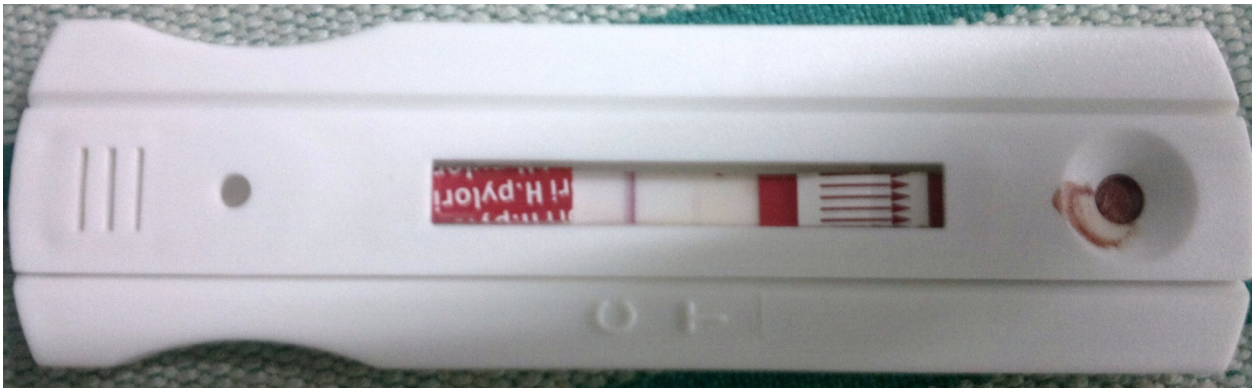


Fig 2 : Serology Card Showing Negative result



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PROFORMA

NAME :

AGE :

SEX :

INPATIENT NO. :

COMPLAINTS :

DURATION OF COMPLAINTS :

DIAGNOSIS :

PREVIOUS TREATMENT :

SMOKING / ALCOHOL USE :

H.PYLORI SEROLOGY :

UPPER GI ENDOSCOPY :

Ref. No. 01104 /E4/3/2012

Govt.Rajaji Hospital,Madurai.20.
Dated: 13.03.2012

Institutional Review Board / Independent Ethics Committee.
Dr. A. Edwin Joe, M.D (FM), BL.,
Dean, Madurai Medical College & 2521021 (Secy)
Govt Rajaji Hospital, Madurai 625020.
Convenor
grhethicssecy @gmail.com.

Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding.

The next Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 11.00 Am to 1.00Pm on 23.02.2012 at the Dean Chamber, Govt. Rajaji Hospital, Madurai. The following members of the committee have been attended the meeting.

1. Dr.N.Vijayasankaran,M.ch(Uro.) 094-430-58793 0452-2584397	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
2. Dr.P.K. Muthu Kumarasamy, M.D., 9843050911	Professor & H.O.D of Medical, Oncology(Retired)	Member Secretary
3. Dr.T.Meena,MD 094-437-74875	Professor of Physiology, Madurai Medical College	Member
4. Dr. S. Thamilarasi, M.D (Pharmacol)	Professor of pharmacology	
5.Dr.Moses K.Daniel MD(Gen.Medicine) 098-421-56066	Professor of Medicine Madurai Medical College	Member
6.Dr.M.Gobinath,MS(Gen.Surgery) 097-871-50040	Professor of Surgery Madurai Medical College	Member
7.Dr.S. Dilshadh, MD(O&G)	Professor of OP&Gyn Madurai Medical College	Member
8.Dr.S.Vadivel Murugan., M.D, 097-871-50040	Professor of Medicine Madurai Medical College	Member
9.Shri.M.Sridher,B.sc.B.L. 099-949-07400	Advocate, 623-B.II.Floor,East II Cross, K.K.Nagar,Madurai.20.	Member
10.Shri.O.B.D.Bharat,B.sc., 094-437-14162	Businessman Plot No.588, K.K.Nagar,Madurai.20.	Member
11.Shri. S.sivakumar,M.A(Social) Mphil 093-444-84990	Sociologist, Plot No.51 F.F, K.K Nagar, Madurai.	Member

Following Projects were approved by the committee

Sl. No	Name of P.G.	Course	Name of the Project	Remarks
1.	Rajarajan. K	PG, M.S (genl surg)	Prevalence of H. pylor in acid peptic disease.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.
She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.
4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8.She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

DEAN

12/3/12

To
All the above members and Head of the Departments concerned.
All the Applicants.

MASTER CHART

No	Name	A/S	IP No.	Complaints	Duration	Diagnosis	Previous Treatment	Addictions	Serology	OGD
1	Jeya Pandi	34/M	14217	Epigastric Pain	1 year	Gastric Perforation	OTC Antacids	Smoker	Negative	Not Done
2	Kasinathan	45/M	77882	Pain Abdomen	15 years	Acid Peptic Disease	OTC Antacids	Nil	Positive	Active Bulbar Ulcer
3	Palani	51/M	76290	Heart Burn	20 years	Chr.DU with GOO	Native	Alcoholic	Positive	Deformed Duodenal Bulb
4	Veeranan	51/M	20914	Pain Abdomen	2 years	Chr.DU with GOO	OTC Antacids	Smoker	Positive	Deformed Duodenal Bulb
5	Muthiah	50/M	82993	Pain Abdomen	8 days	DU Perforation	Nil	Nil	Negative	Not Done
6	Ponram	60/M	9388	Pain Abdomen	1 day	DU Perforation	Nil	Alcoholic	Positive	Not Done
7	Thiraviyam	35/M	3747	Pain Abdomen	2 days	Du Perforation	Nil	Nil	Positive	Not Done
8	Gandhi	30/M	77135	Vomiting	15 days	Chr.DU with GOO	OTC Antacids	Nil	Positive	Oesophagitis-Du Ulcer-GOO
9	Dinesh	36/M	75643	Heart Burn	6 months	Non Ulcer Dyspepsia	OTC Antacids	Nil	Positive	Normal Study
10	Paramasivam	58/M	18782	Malena	7 days	Acid Peptic Disease	OTC Antacids	Smoker	Positive	Deformed Duodenal Bulb
11	Ragupathi	70/M	63318	Pain Abdomen	5 days	DU Perforation	OTC Antacids	Smoker	Negative	Not Done
12	Natarajan	38/M	3911	Pain Abdomen	6 months	DU Perforation	OTC Antacids	Nil	Positive	Active DU
13	Raja	45/M	28134	Pain Abdomen	2 days	DU Perforation	Nil	Smoker	Negative	Not Done
14	Murugesan	40/M	30782	Pain Abdomen	1 day	DU Perforation	OTC Antacids	Nil	Positive	Not Done
15	Jeya Pandi	48/M	14217	Pain Abdomen	4 days	Gastric Perforation	Nil	Nil	Negative	Not Done
16	Veeramakali	70/M	29780	Pain Abdomen	10 days	Chr.DU with GOO	OTC Antacids	Nil	Positive	Deformed Duodenal Bulb
17	Andisamy	50/M	66641	Pain Abdomen	4 years	Acid Peptic Disease	Nil	Smoker	Positive	Erosive Antral Gastritis
18	Vijayan	29/M	66630	Heart Burn	8 months	Acid Peptic Disease	OTC Antacids	Nil	Negative	Bulbar DU Ulcer
19	Thangaraj	35/M	35680	Pain Abdomen	5 days	DU Perforation	Nil	Smoker	Negative	Not Done
20	Sundarajan	50/M	44283	Pain Abdomen	5 years	Chr.DU with GOO	OTC Antacids	Smoker	Negative	Active DU Ulcer

21	Nagaraj	36/M	22816	Epigastric Pain	2 years	Acid Peptic Disease	OTC Antacids	Alcoholic	Positive	Oesophagitis with DU Ulcer
22	Kannan	29/M	24214	Heart Burn	1 year	Acid Peptic Disease	OTC Antacids	Nil	Positive	Oesophagitis
23	Sakkarai	44/M	27884	Vomiting	1 month	Chr.DU with GOO	OTC Antacids	Alcoholic	Positive	Deformed Duodenal Bulb
24	Pandi	58/M	30532	Vomiting	1 month	Carcinoma Stomach	Nil	Smoker	Positive	Ulcer Growth Distal Stomach
25	Raja	35/M	30753	Pain Abdomen	2 days	DU Perforation	Nil	Nil	Negative	Not Done
26	Murugesan	45/M	30782	Pain Abdomen	2 days	DU Perforation	OTC Antacids	Alcoholic	Positive	Not Done
27	Sivalingam	53/M	74921	Epigastric Pain	7 days	Acid Peptic Disease	Nil	Alcoholic	Positive	Active DU Ulcer
28	Ramanathan	40/M	30441	Pain Abdomen	2 days	DU Perforation	OTC Antacids	Nil	Positive	Not Done
29	Saravanan	45/M	32158	Pain Abdomen	6 months	Acid Peptic Disease	OTC Antacids	Nil	Positive	Active DU Ulcer
30	Vellaisamy	48/M	32384	Pain Abdomen	6 months	Non Ulcer Dyspepsia	Nil	Nil	Negative	Normal Study
31	Bose	66/M	34230	Loss of Apetite	6 months	Carcinoma Stomach	Nil	Alcoholic	Positive	Antral Growth
32	Venkatesh	36/M	36354	Epigastric Pain	2 months	Acid Peptic Disease	Nil	Nil	Negative	Gastritis
33	Zahir Hussain	27/M	38111	Pain Abdomen	1 day	DU Perforation	OTC Antacids	Nil	Positive	Not Done
34	Soundarapandi	45/M	45425	Loss of Apetite	1 month	Carcinoma Stomach	Nil	Nil	Negative	Ulcer Growth Distal Stomach
35	Sevugamurthy	38/M	51599	Pain Abdomen	1 month	Non Ulcer Dyspepsia	OTC Antacids	Nil	Negative	Normal Study
36	Sakthi	30/M	58383	Pain Abdomen	1 year	Non Ulcer Dyspepsia	OTC Antacids	Nil	Negative	Normal Study
37	Arokiam	52/M	9244	Pain Abdomen	2 days	DU Perforation	Nil	Nil	Positive	Not Done
38	Saravanan	30/M	70849	Heart Burn	6 months	Acid Peptic Disease	Nil	Alcoholic	Positive	Deformed Duodenal Bulb
39	Thomas	38/M	61769	Loss of Apetite	1 month	Carcinoma Stomach	Nil	Nil	Negative	Ulcer Growth Distal Stomach
40	Kannan	39/M	63377	Epigastric Pain	2 months	Acid Peptic Disease	OTC Antacids	Nil	Negative	Duodinitis+Esophagitis
41	Chinnamannan	38/M	63614	Pain Abdomen	1 day	DU Perforation	Nil	Nil	Negative	Not Done
42	Pandi	58/M	69636	Pain Abdomen	1 day	DU Perforation	Nil	Nil	Negative	Not Done
43	Kulandaivel	30/M	71327	Vomiting	1 month	Chr. DU with GOO	OTC Antacids	Alcoholic	Positive	Deformed Duodenal Bulb

44	Ayyavu	65/M	74420	Epigastric Pain	4 months	Non Ulcer Dyspepsia	OTC Antacids	Nil	Positive	Normal Study
45	Muneeswaran	30/M	81671	Epigastric Pain	1 month	Non Ulcer Dyspepsia	OTC Antacids	Nil	Negative	Normal Study
46	Murugan	55/M	81697	Pain Abdomen	6 months	Acid Peptic Disease	OTC Antacids	Nil	Negative	Gastritis
47	Chellapanddi	29/M	777	Pain Abdomen	4 days	DU Perforation	Nil	Smoker	Positive	Not Done
48	Veeran	45/M	3924	Pain Abdomen	2 days	DU Perforation	Nil	Nil	Negative	Not Done
49	Ayyavu	62/M	7435	Pain Abdomen	1 day	DU Perforation	Nil	Nil	Positive	Not Done
50	Padmanaban	55/M	7669	Pain Abdomen	2 days	DU Perforation	Nil	Smoker	Positive	Not Done
51	Adaikalam	65/F	24961	Vomiting	1 month	Chr.DU with GOO	OTC Antacids	Nil	Positive	Deformed DU Bulb
52	Sowmiya	19/F	32162	Pain Abdomen	2 months	Non Ulcer Dyspepsia	OTC Antacids	Nil	Negative	Normal Study
53	Dhanalakshmi	50/F	39885	Pain Abdomen	3 months	Acid Peptic Disease	OTC Antacids	Nil	Negative	Duodinitis
54	Sindhu	18/F	6114	Pain Abdomen	2 months	Acid Peptic Disease	OTC Antacids	Nil	Negative	Gastritis
55	Janaki	52/F	6165	Epigastric Pain	1 month	Acid Peptic Disease	Nil	Nil	Positive	Active Bulbar Ulcer
56	Sarasu	55/F	7177	Loss of Apetite	2 months	Carcinoma Stomach	Nil	Nil	Positive	Growth Distal Stomach
57	Meenakshi	55/F	7209	Mass Abdomen	3 months	Carcinoma Stomach	Nil	Nil	Positive	Antral Growth
58	Velammal	37/F	7446	Vomiting	1 month	Chr.DU with GOO	OTC Antacids	Nil	Positive	Deformed DU Bulb
59	Murugeswari	28/F	7732	Pain Abdomen	1 month	Acid Peptic Disease	Nil	Nil	Positive	Active Bulbar Ulcer
60	Jeya	51/F	10810	Vomiting	15 days	Chr.DU with GOO	OTC Antacids	Nil	Positive	Deformed DU Bulb
61	Ponammal	62/F	14499	Pain Abdomen	2 days	DU Perforation	Nil	Nil	Positive	Not Done
62	Sangammal	35/F	14995	Vomiting	20 days	Chr.DU with GOO	Nil	Nil	Positive	Deformed DU Bulb
63	Asai	23/F	18040	Pain Abdomen	1 day	DU Perforation	Nil	Nil	Positive	Not Done
64	Meena	46/F	26758	Mass Abdomen	1 month	Carcinoma Stomach	Nil	Nil	Negative	Growth Distal Stomach
65	Kaliammal	48/F	14125	Vomiting	1 month	Chr.DU with GOO	Nil	Nil	Positive	Deformed DU Bulb

66	Jeyashanthi	40/F	32637	Pain Abdomen	1 day	DU Perforation	OTC Antacids	Nil	Positive	Not Done
67	Sivapackiam	40/F	38283	Vomiting	20 days	Chr.DU with GOO	Nil	Nil	Negative	Deformed DU Bulb
68	Karugi	45/F	40006	Pain Abdomen	1 day	DU Perforation	Nil	Nil	Positive	Not Done
69	Lalitha	55/F	42199	Pain Abdomen	1 day	DU Perforation	Nil	Nil	Negative	Not Done
70	Bakiam	60/F	45279	Loss of Apetite	2 months	Carcinoma Stomach	Nil	Nil	Negative	Growth Distal Stomach
71	Lakshmi	40/F	47177	Loss of Apetite	2 months	Carcinoma Stomach	Nil	Nil	Positive	Growth Distal Stomach
72	Pechiammal	65/F	50689	Pain Abdomen	2 days	DU Perforation	OTC Antacids	Nil	Positive	Not Done
73	Buvaneshwari	20/F	58987	Pain Abdomen	1 day	DU Perforation	OTC Antacids	Nil	Positive	Not Done
74	Palaniammal	60/F	53303	Pain Abdomen	2 days	DU Perforation	OTC Antacids	Nil	Negative	Not Done
75	Pichaimuthu	23/F	64961	Pain Abdomen	3 days	DU Perforation	OTC Antacids	Nil	Positive	Not Done
76	Guruvammal	85/F	73070	Pain Abdomen	2 months	Acid Peptic Disease	OTC Antacids	Nil	Negative	Antral Gastritis
77	Lillipushpam	43/F	88857	Vomiting	1 month	Chr.DU with GOO	OTC Antacids	Nil	Positive	Cicatrised DU Bulb
78	Kambarbanu	38/F	72803	Heart Burn	6 months	Acid Peptic Disease	OTC Antacids	Nil	Positive	Gastritis
79	Deivathammal	50/F	28362	Epigastric Pain	1 year	Acid Peptic Disease	OTC Antacids	Nil	Positive	Active Bulbar Ulcer
80	Amutha	45/F	37472	Epigastric Pain	6 months	Acid Peptic Disease	OTC Antacids	Nil	Positive	Active Bulbar Ulcer
81	Selvapriya	22/F	41159	Epigastric Pain	2 months	Acid Peptic Disease	OTC Antacids	Nil	Positive	Active Bulbar Ulcer
82	Vanitha	28/F	43233	Pain Abdomen	1 year	Acid Peptic Disease	OTC Antacids	Nil	Positive	Cicatrised DU Bulb
83	Muthulaxmi	39/F	38662	Pain Abdomen	3 days	DU Perforation	OTC Antacids	Nil	Negative	Not Done
84	Pandiammal	21/F	16088	Pain Abdomen	1 day	DU Perforation	OTC Antacids	Nil	Positive	Not Done
85	Shanmugavalli	30/F	53245	Pain Abdomen	2 days	DU Perforation	OTC Antacids	Nil	Positive	Not Done
86	Rathnammal	37/F	54830	Pain Abdomen	1 day	DU Perforation	OTC Antacids	Nil	Negative	Not Done
87	Palayi	60/F	58012	Vomiting	1 month	Chr.DU with GOO	Nil	Nil	Positive	Cicatrised DU Bulb
88	Chellammal	63/F	51319	Vomiting	2 months	Chr.DU with GOO	OTC Antacids	Nil	Positive	Deformed DU Bulb

89	Soundaravalli	29/F	54898	Pain Abdomen	2 days	DU Perforation	Nil	Nil	Positive	Not Done
90	Mahalakshmi	27/F	114290	Epigastric Pain	3 weeks	Acid Peptic Disease	OTC Antacids	Nil	Negative	Pangastritis
91	Tamilarasi	45/F	114558	Epigastric Pain	6 months	Acid Peptic Disease	OTC Antacids	Nil	Negative	Antral Gastritis
92	Mariammal	45/F	79729	Pain Abdomen	3 days	DU Perforation	OTC Antacids	Nil	Negative	Not Done
93	Meenakshi	50/F	79110	Epigastric Pain	3 months	Carcinoma Stomach	OTC Antacids	Nil	Positive	Antral Growth
94	Ragupathy	70/F	93318	Pain Abdomen	5 days	DU Perforation	OTC Antacids	Tobacco	Positive	Not Done
95	Arumugathal	62/F	24414	Hemetemesis	2 days	Acid Peptic Disease	OTC Antacids	Nil	Positive	Prepyloric Ulcer + DU Ulcer
96	Sundarajam	50/F	44283	Pain Abdomen	5 years	Chr.DU with GOO	OTC Antacids	Tobacco	Negative	Cicatrised DU Bulb
97	Said Ali Fatima	33/F	36925	Pain Abdomen	3 years	Acid Peptic Disease	OTC Antacids	Nil	Negative	Antral Gastritis
98	Sathya	23/F	55991	Pain Abdomen	1 year	Non Ulcer Dyspepsia	OTC Antacids	Nil	Negative	Normal Study
99	Deivanai	15/F	58908	Pain Abdomen	6 months	Non Ulcer Dyspepsia	OTC Antacids	Nil	Negative	Normal Study
100	Sangumani	29/F	49639	Pain Abdomen	3 months	Acid Peptic Disease	OTC Antacids	Nil	Positive	Active Bulbar Ulcer